

Aromatic Trifluoromethylation with Metal Complexes

Olesya A. Tomashenko and Vladimir V. Grushin*

The Institute of Chemical Research of Catalonia (ICIQ), Tarragona 43007, Spain

CONTENTS

1. Introduction	A
2. Trifluoromethyl Sources	C
3. Trifluoromethyl and Perfluoroalkyl Derivatives of Catalytic Metals: Synthesis, Bonding, and Reactivity	D
3.1. A Brief Overview of Metal Perfluoroalkyls	D
3.2. Electronic Effects of CF ₃ : Is It an Electron Acceptor or Donor?	E
3.3. Copper	G
3.4. Palladium	I
3.5. Nickel	L
4. Stoichiometric Ar–CF ₃ Bond Formation with Metals	L
4.1. Copper-Promoted Reactions	M
4.1.1. Polyfluorinated Methanes as CF ₃ Sources	M
4.1.2. Trifluoroacetic and Fluorosulfonyldifluoroacetic Acid Derivatives as CF ₃ Sources	O
4.1.3. Trifluoromethylcopper Reagents via Transmetalation	R
4.1.4. Ruppert's Reagent CF ₃ SiMe ₃ and its Ethyl Analogue CF ₃ SiEt ₃	S
4.1.5. Well-Defined CF ₃ Cu Complexes	T
4.2. Ar–CF ₃ Bond Formation at Palladium and Nickel Centers	AE
5. Metal-Catalyzed Aromatic Trifluoromethylation Reactions	AG
6. Aromatic Perfluoroalkylation with Higher R _f	AK
7. Conclusions and Outlook	AM
8. Latest Developments	AO
Author Information	AO
Biographies	AO
Acknowledgment	AO
Abbreviations	AP
References	AP

1. INTRODUCTION

"All new is well-forgotten old", the proverb goes. The current "fluorine boom"¹ is news only to a novice in the field: the exceptional importance of fluorinated organic compounds in numerous areas has been known for a long time. The sharpest increase in the number of fluorine-containing pharmaceuticals² and agrochemicals³ is dated back to 30 years ago. Also around that time (1979), the first monograph⁴ devoted to industrial applications of organofluorine compounds was published, covering not only fluorine-containing biologically active materials but

also refrigerants, propellants, surfactants, textile chemicals, polymers, and dyes.

The increasingly broad realization of the key role of organofluorine compounds in numerous areas has recently attracted many new scientists to the field. The development of new methods for the selective introduction of fluorine and fluorine-containing groups into organic molecules for biologically active and other useful materials has become a hot area. Over 100 reviews, book chapters, and highlights on this subject have appeared in the literature in the past few years. As citing all of these publications in this review article is impossible, we provide references to only the most recent, general, and comprehensive ones.^{2–17}

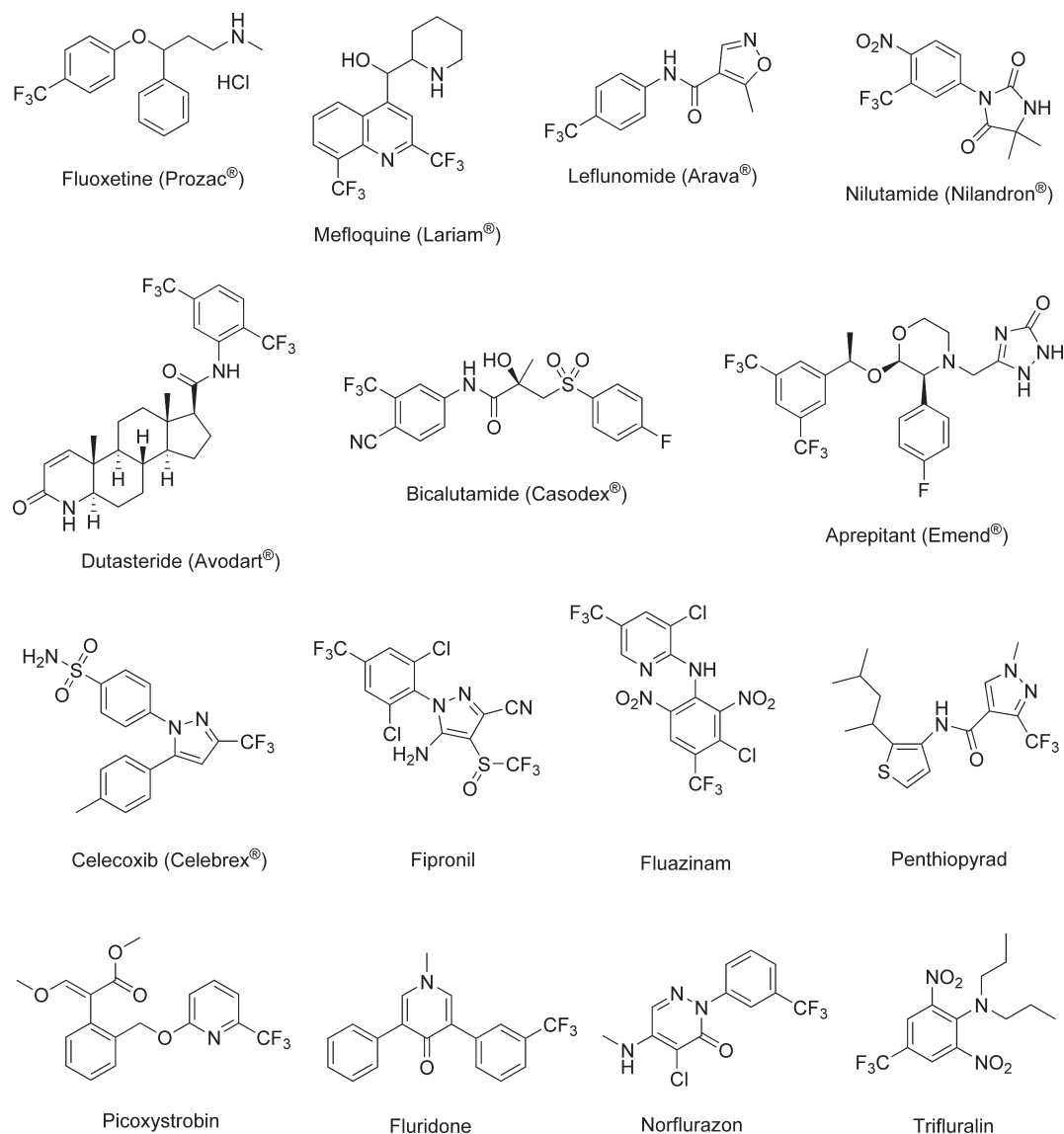
Molecules bearing a trifluoromethyl group constitute one of the most important classes of selectively fluorinated compounds. As early as 1928, Lehmann¹⁸ reported his observations of biological activity of some trifluoromethylated organic derivatives and already in 1959 Yale¹⁹ published a detailed review article entitled "The Trifluoromethyl Group in Medicinal Chemistry". Since then, numerous books and reviews have appeared in the literature covering various aspects of trifluoromethylated organic^{20–46} and organometallic^{32,43,45,47,48} compounds. Within this family, derivatives bearing the CF₃ group on aromatic rings are particularly numerous and important. Some examples of such compounds used as active ingredients of pharmaceuticals and agrochemicals are shown in Scheme 1.

Trifluoromethylated building blocks and intermediates are clearly needed to make such molecules. The simplest trifluoromethylated aromatic compound, benzotrifluoride, was originally prepared by Swarts⁴⁹ at the end of the 19th century. In his work, Swarts treated benzotrichloride with "two thirds of its weight of antimony fluoride" to obtain a mixture of PhCF₂Cl and PhCF₃, from which the two were separated and isolated pure by distillation. In the early 1930s, two industrial groups, one from Kinetic Chemicals, Inc.⁵⁰ and one from I. G. Farbenindustrie AG⁵¹ patented their discoveries on the successful use of HF instead of SbF₃ for the Swarts reaction. These inventions were the starting point for the modern large-scale manufacturing of trifluoromethylated aromatics. Other methods have been developed for conversion of various C1 units on the ring to CF₃ with a variety of fluorinating agents.^{20–23,38,44,52}

While representing an outstanding discovery and a classic of organic and organofluorine chemistry, the Swarts reaction is nonetheless neither atom-economical nor environmentally benign, as it deals with stoichiometric quantities of hazardous chemicals and generates large amounts of chlorine waste. To convert a CH₃ group on the ring to CF₃, the methyl is first exhaustively chlorinated to produce 3 equiv of HCl as a

Received: December 15, 2010

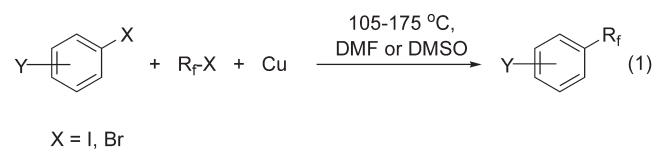
Scheme 1



byproduct. The CCl_3 derivative is then fluorinated to coproduce 3 more equiv of HCl per each equivalent of the desired trifluoromethylated compound. By stoichiometry, 3 equiv of Cl_2 are consumed and 6 equiv of HCl are generated per each equivalent of the aromatic trifluoromethylated product made. In reality, however, the quantity of the chlorine waste produced is commonly superstoichiometric, because the yields are not quantitative. The Swarts reaction nonetheless still remains the only method for large-scale manufacturing of trifluoromethylaromatics, entirely because of the lack of an industrially feasible alternative.

A totally different approach to the synthesis of trifluoromethylated aromatic compounds is based on the introduction of the CF_3 group into the aromatic ring. Radical perfluoroalkylation of aromatic compounds has been known for a long time.⁴⁴ However, as was demonstrated as early as 1960,⁵³ the formation of diperfluoroalkylated side products is hard to avoid, even if the arene substrate is used in a large excess. Furthermore, radical perfluoroalkylation reactions, as expected, usually exhibit poor positional selectivity,^{54a–f} although a limited number of exceptions exist.^{54a,b,g–i}

On May 21, 1965, McLoughlin and Thrower applied for a patent to protect their groundbreaking invention of the first metal-mediated polyfluoroalkylation of aromatic compounds. In 1968, the U.S. Patent was issued,⁵⁵ and a detailed full report followed quickly to appear in the open literature in 1969.⁵⁶ McLoughlin and Thrower discovered that polyfluoroalkyl iodides reductively couple with iodoarenes in the presence of copper to produce the corresponding polyfluoroalkylaromatic compounds (eq 1). Much higher conversions, yields, and selectivities were obtained for $\text{X} = \text{I}$ than for $\text{X} = \text{Br}$. Importantly, it was found that the incoming perfluoroalkyl group always appeared on the carbon atom originally bearing the halogen substituent.



Although the McLoughlin–Thrower reaction (eq 1) employs stoichiometric amounts of copper and costly iodinated starting

materials, its importance to the field is difficult to overestimate. The very possibility of selective aromatic perfluoroalkylation opened up a new area for research toward the development of an industrially viable alternative to the Swarts reaction. Unsurprisingly, therefore, the discovery of the Cu-mediated aromatic perfluoroalkylation (eq 1) immediately prompted further work in the area. Already in 1969, Kobayashi and Kumadaki⁵⁷ preliminarily communicated their optimization of the reaction for $R_f = CF_3$ and preparation of a series of trifluoromethylated arenes and heteroarenes, following the McLoughlin–Thrower lead.⁵⁵

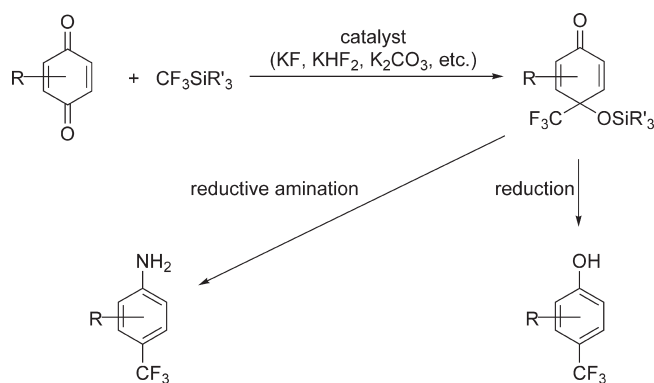
Since the late 1960s, the area of aromatic trifluoromethylation with metals has been continuously growing. Results of these studies by numerous research groups have been described in a number of surveys, including the particularly in-depth review articles by Burton and Yang (1992),⁴⁵ McClinton and McClinton (1992),⁴⁴ Burton and Lu (1997),⁴³ and more recently by Schlosser (2006),³⁸ Davis and Burton (2009),³² and Kumadaki's group (2010).²⁹ A recent brief essay on the subject by Fors⁵⁸ is available online. In the last 5 years, however, particularly significant progress has been made in the field. The most recent achievements include the first examples of Ar–CF₃ bond formation at a Pd(II) center⁵⁹ and with a well-defined Cu(I) complex⁶⁰ as well as aromatic trifluoromethylation reactions that are catalytic in copper^{61,62} and palladium.^{63,64} Some of these results have been briefly highlighted⁶⁵ and one of us has recently reviewed his own work in the area.⁶⁶ A few sketchy essays on aromatic trifluoromethylation have recently appeared in the Chinese and Japanese literature.⁶⁷ However, we are unaware of an overview that provides a comprehensive coverage of aromatic trifluoromethylation and perfluoroalkylation reactions with metals, including recent achievements in the area.

The goal of this review article is to describe and analyze, in considerable detail, aromatic C–CF₃ and C–R_f bond-forming reactions using metals and their complexes in both stoichiometric and catalytic amounts. Special attention will be paid to organometallic and mechanistic aspects of the chemistry, as we strongly believe that those are of particular importance for further progress in the field. We will also provide an outlook for future studies with emphasis on practical features and requirements for industrial feasibility. Selective difluoromethylation and monofluoromethylation reactions that have been recently reviewed,⁶⁸ asymmetric trifluoromethylation,⁴¹ and radical perfluoroalkylation⁵⁴ are beyond the scope of this article.

2. TRIFLUOROMETHYL SOURCES

In 2007, Ma and Cahard³⁶ published a review entitled “Strategies for Nucleophilic, Electrophilic, and Radical Trifluoromethylations”. Although aromatic trifluoromethylation is not covered in the Ma–Cahard overview, the article presents an elaborate classification and uses of all three types of trifluoromethylating reagents. Most recently, stable electrophilic trifluoromethylating reagents were thoroughly reviewed.²⁸ However, electrophilic^{28,69} and radical^{44,54} metal-promoted aromatic perfluoroalkylation reactions are rare. It is worth noting that although some radical perfluoroalkylation reactions employ metal compounds (e.g., Cu,^{54c,g,h} Zn,^{54d–f} and Fe⁵⁴ⁱ), the metals are not directly involved in the Ar–R_f bond-forming step but rather are needed to generate the perfluoroalkyl radical from R_fX (X = I, Br). As the main subject of this review is trifluoromethylation

Scheme 2



of nonactivated aromatic electrophiles, we will focus mainly on CF₃ sources for those metals that are particularly capable of efficiently activating the poorly reactive Ar–X bonds (X = I, Br, Cl, OTf, etc.): palladium, copper, and nickel.

Trifluoromethyl iodide (CF₃I), bromide (CF₃Br), and other perfluoroalkyl halides have been widely used to synthesize various transition metal^{47,48} and main group^{43,45,70} organometallic compounds. The first metal-promoted perfluoroalkylation of haloarenes (eq 1)^{55,56} employed the “R_fCu” reagents prepared from R_fI and copper metal.

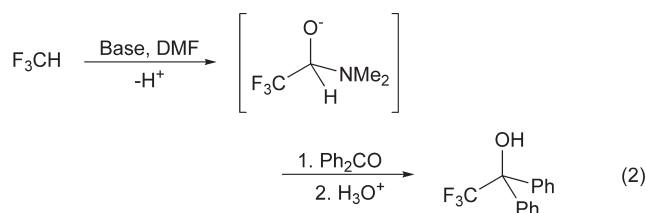
Trifluoromethyl silicon compounds of the general formula CF₃SiR₃ (R = alkyl) have become particularly popular in both organic and organometallic synthesis. The most used reagent for a broad variety of trifluoromethylation reactions is CF₃SiMe₃, which is often referred to as Ruppert’s reagent or the Ruppert–Prakash reagent. Five years after the original report by Ruppert et al.⁷¹ on the synthesis of CF₃SiMe₃ in 1984, the compound was shown to cleanly trifluoromethylate electrophiles. In 1989, Kruse et al.,⁷² Prakash et al.,⁷³ and Stahly⁷⁴ reported a series of trifluoromethylation reactions of carbonyl compounds and quinones with CF₃SiR₃. Interestingly, Stahly’s research⁷⁴ was aimed at the synthesis of otherwise hardly accessible 4-trifluoromethylated phenols and anilines. We present this elegant work by Stahly herein (Scheme 2), despite the fact that the bond formation between the CF₃ group and the “aromatic to be” carbon is not metal-promoted and is limited to only certain isomers of trifluoromethylated phenols and anilines.

Applications of Ruppert’s reagent in synthesis have been extensively reviewed.^{37,42,75–78} Since the demonstration of successful trifluoromethyl transfer from CF₃SiMe₃ to main group⁷⁹ and transition⁸⁰ metal centers, Ruppert’s reagent has been widely used for the synthesis of trifluoromethyl metal compounds (section 3) and trifluoromethylated aromatics. Ruppert’s reagent and its analogues are currently the most popular CF₃ and R_f sources for aromatic trifluoromethylation (sections 4.1.4 and 5) and perfluoroalkylation (section 6).

Trifluoroacetic acid salts and derivatives (CF₃CO₂X, where X = Na, K, Me, etc.) are attractive CF₃ sources. It has been known since 1981 that alkali metal trifluoroacetates can transfer the CF₃ group to copper upon decarboxylation to produce CuCF₃ species that can trifluoromethylate aryl halides.⁸¹ Since the original publication, a considerable number of papers have appeared in the literature reporting the use of alkali metal trifluoroacetates and also methyl trifluoroacetate⁸² (section 4.1.2). Although cost-wise alkali metal trifluoroacetates are much

more attractive than most of the reagents described above, there are certain problems associated with their use,⁸² including the necessity to employ them in large excess to achieve good yields.

Trifluoromethane or fluoroform (CF_3H)⁸³ is, perhaps, the most attractive CF_3 source. A side-product in Teflon[®] manufacturing, fluoroform is readily available, inexpensive, atom-economical, nontoxic, and not ozone-depleting.^{84–86} Fluoroform is a gas (bp = ca. $-82\text{ }^\circ\text{C}$)⁸⁷ that is easily soluble in many organic solvents. There have been only a limited number of publications reporting the use of CHF_3 as a CF_3^- anion synthon.^{84–86,88–93} Trifluoromethane is a weak acid ($\text{p}K_{\text{a}} = 27$ in water),⁹⁴ considerably less acidic than chloroform. Therefore, a strong base such as dimethyl potassium or *t*-BuOK is required to deprotonate CHF_3 . To avoid the notoriously facile formation of difluorocarbene, the deprotonation is conventionally performed at a low temperature in DMF to form a more stable hemiaminolate that is then used in situ for reactions with electrophiles, such as carbonyl compounds^{84,85,88–93} (e.g., eq 2).



Numerous attempts to directly cuprate or zincate fluoroform have failed.⁸⁵ However, multistep procedures to indirectly generate CF_3Cu from CF_3H have been reported^{85,86} and are described in section 4.1.1 below.

Difluoromethyl derivatives (CF_2Cl_2 , CF_2ClBr , CF_2Br_2 , $\text{CF}_2\text{ClCO}_2\text{X}$, etc.) can sometimes be very efficient CF_3 sources. In 1985, Burton and Wiemers⁹⁵ reported a remarkably simple and high-yielding (80–95%) preparation of trifluoromethyl Zn and Cd reagents from the corresponding metal and CF_2X_2 ($\text{X} = \text{Br}, \text{Cl}$) in DMF. The proposed mechanism involves the formation of difluorocarbene via electron transfer to the polyhalomethane from the metal, followed by fluoride addition to give “ CF_3^- ”. The fluoride source is the ionized form of HCF_2NMe_2 that is produced, along with a molecule of CO, from DMF and CF_2 . Decarboxylative trifluoromethylations have also been developed.^{96–98} Methyl fluorosulfonyldifluoroacetate $\text{FSO}_2\text{CF}_2\text{CO}_2\text{Me}$ ⁹⁹ is a commercially available reagent that has been found¹⁰⁰ to efficiently generate CF_3Cu upon decarboxylation and loss of SO_2 .

Other CF_3 sources are available, including fluoral and its derivatives.⁹³ Apart from their efficiency, toxicity, and ease of handling, commercial trifluoromethyl sources should also be considered from the perspective of availability and cost. An oversimplified cost comparison was most recently presented for eight commercially available CF_3 sources.¹⁰¹ All prices in US dollars per mole were calculated using the 2009–2010 Aldrich catalogue for the largest available quantities, including CF_3SiMe_3 (\$2254.40), CF_3SiEt_3 (\$11 789.70), CF_3I (\$755.23), and trifluoroacetic acid (\$23.70). Although these figures are far from the bulk market prices, they provide some comparison of the costs. A number of trifluoromethyl sources are on the Montreal Protocol list of substances that deplete the ozone layer,¹⁰² including CF_3Cl , CF_3Br , CF_2Cl_2 , CF_2ClBr , and CF_2Br_2 . As a result, the availability of, and access to, some of these materials for research are limited in certain countries.

3. TRIFLUOROMETHYL AND PERFLUOROALKYL DERIVATIVES OF CATALYTIC METALS: SYNTHESIS, BONDING, AND REACTIVITY

In this section, we will first provide a brief general overview of metal perfluoroalkyls, including their synthesis, general properties, and reactivity patterns. Special attention will be paid to electronic and steric effects of CF_3 as a ligand. This analysis will then be followed by a more detailed discussion of perfluoroalkyl derivatives of Cu, Pd, and Ni, the metals that can activate aromatic carbon–halogen bonds and hence are of particular importance to the subject of this review article.

3.1. A Brief Overview of Metal Perfluoroalkyls

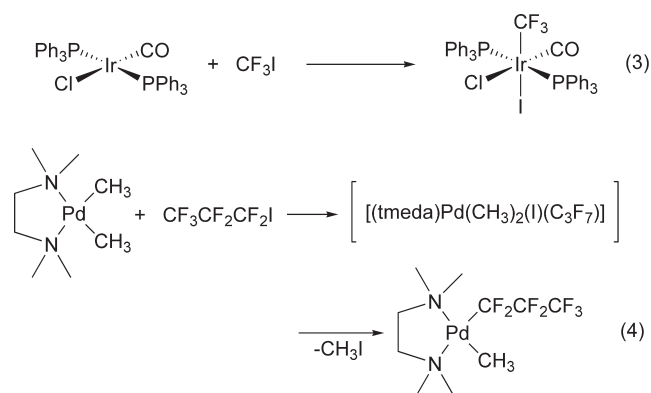
Physical properties of a CF_3 group are compiled in the review article by McClinton and McClinton⁴⁴ and will be summarized herein only briefly. The van der Waals radius and volume of CF_3 are considerably larger than those of CH_3 : 2.7 Å and 42.5 Å³ vs 2.0 Å and 16.8 Å³, respectively.¹⁰³ The trifluoromethyl group is highly lipophilic, as follows from its hydrophobicity parameter value of 1.07 that is considerably higher than that of CH_3 (0.51) but lower than for *t*-Bu (1.68).⁴⁴

As discussed in detail in recent monographs,^{20–23} perfluoroalkyl groups, CF_3 included, form strong and usually poorly reactive bonds to carbon atoms in organic molecules. On the other hand, the stability of metal perfluoroalkyls strongly depends on the nature of both the R_f and the metal, as described and analyzed in a number of reviews on perfluoroalkyl derivatives of both the main group elements^{32,43,45,70} and the transition metals.^{47,48,104–106} In general, the $\text{M}-\text{R}_f$ bonds are considerably stronger and much less reactive than those of the conventional, nonfluorinated metal alkyls. Hughes⁴⁷ writes: “It is now well accepted that compounds containing metal-perfluoroalkyl ($\text{M}-\text{R}_f$) bonds are in some ways less reactive and are invariably more thermally stable than analogues containing hydrocarbon alkyl ($\text{M}-\text{R}$) linkages.” Although in most instances the metal–carbon bond is shorter for $\text{M}-\text{CF}_3$ than for the analogous $\text{M}-\text{CH}_3$ species, this is not always the case.^{60,107} The C–F bonds in metal trifluoromethyls are usually longer and weaker than in organic CF_3 derivatives.

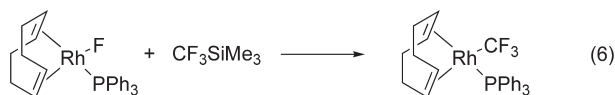
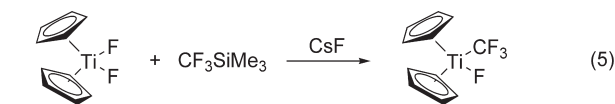
There are many methods to synthesize metal perfluoroalkyls.^{32,43,45,47,48,70,104–106} These include Klabunde’s metal atom condensation with perfluoroalkyl halides¹⁰⁸ and reactions of various metal species with CF_3 radicals generated from the glow discharge of C_2F_6 , developed by Lagow.¹⁰⁹ These methods require special equipment and have been reviewed,⁴⁸ so they will not be considered herein. The most general and widely used routes to metal perfluoroalkyls include (i) oxidative addition of polyfluorohaloalkanes to metals and their complexes, (ii) transmetalation, and (iii) decarboxylation and decarbonylation of metal perfluoroalkylcarboxylates and perfluoroacyls.

Formally an oxidative addition, the reaction of polyfluoroalkyl halides with metals has been widely used to prepare R_fM compounds. It is this method that was used by Emeleus and Hazeldine¹¹⁰ over 60 years ago to synthesize the first metal trifluoromethyl derivatives, $(\text{CF}_3)_2\text{Hg}$ and CF_3HgI , from CF_3I and amalgams of Cd, Zn, Ag, Cu, and Mg. Reactions of polyfluoroalkyl halides with metal powders have found broad use in the generation of R_fCu species, as described in the original McLoughlin–Thrower report,⁵⁶ and Zn and Cd trifluoromethyls from CF_2X_2 ($\text{X} = \text{Br}, \text{Cl}$).⁹⁵ Two types of oxidative addition reactions of R_fX ^{48,104} to coordinatively unsaturated metal complexes are exemplified by eqs 3¹¹¹ and 4.¹¹² The

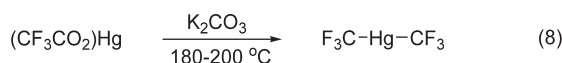
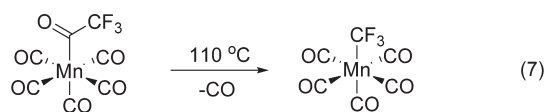
reaction of Vaska's complex with CF_3I leads to an Ir(III) adduct that is stable and can be isolated; evidence has been presented for the adduct being trans.¹¹¹ In the other type of R_fX oxidative addition, the transient high-valent complex is unstable and undergoes reductive elimination that does not involve the just formed $\text{M}-\text{R}_f$ bond. This is the case with the transformation shown in eq 4, where the highly unstable Pd(IV) intermediate instantly reductively eliminates methyl iodide.¹¹²



Transmetalation, that is, R_f transfer from one metal (element) to another, is probably the most widely used laboratory method to prepare metal perfluoroalkyls. Several $\text{M}-\text{CF}_3$ sources have been developed and proven useful for the synthesis of trifluoromethyl derivatives of other elements. These include CF_3 transfer from Morrison's $(\text{CF}_3)_2\text{Cd} \cdot \text{DME}$ to a variety of metals^{48,113} and the synthesis of trifluoromethyl copper using CF_3 derivatives of Hg, Cd, and Zn.^{43–45,95,114} Over the past decade, however, commercially available Ruppert's reagent has become by far the most widely used source of CF_3 to synthesize trifluoromethyl metal complexes. This method is general, as exemplified by the two reactions involving an early (eq 5)¹¹⁵ and a late (eq 6)¹¹⁶ transition metal. The synthesis of Cu, Pd, and Ni trifluoromethyl complexes with Ruppert's reagent will be discussed in detail in sections 3.3–3.5 below.

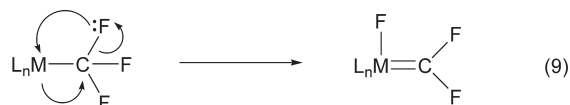


Decarbonylation of perfluoroacyl derivatives is the method that was used to prepare the first CF_3 complex of a d-block metal (eq 7).¹¹⁷ An excellent, high-yielding decarboxylation method has been developed by Dyatkin et al.¹¹⁸ for the synthesis of $(\text{CF}_3)_2\text{Hg}$ from $(\text{CF}_3\text{CO}_2)\text{Hg}$ (eq 8).

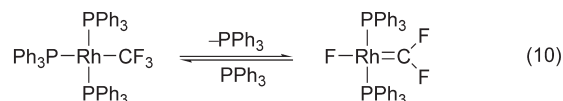


The most characteristic transformation of the CF_3 ligand is α -elimination leading to a carbene species (eq 9). The latter can be extremely unstable, even at very low temperatures, instantaneously decomposing to MF and CF_2 , as is the case with CF_3Li ,⁴⁵

or stable and isolable, as often is the case with a number of transition metal complexes.^{47,48,104} Mechanistically, α -elimination may be viewed as intramolecular nucleophilic attack of a fluorine atom of the CF_3 ligand on the metal. The process could also be rationalized¹⁰⁶ in terms of interaction of the filled d orbitals on the metal with the antibonding orbital of the $\text{C}-\text{F}$ σ -bond, so-called "negative hyperconjugation" or $\text{M}(\text{d}_\pi)-\text{CF}_3(\sigma^*)$ back-donation. It is noteworthy, however, that in the ground state such interactions are weak. Importantly, difluorocarbene (and other dihalocarbenes) on the metal can exhibit both electrophilic and nucleophilic behavior, and hence, such complexes are difficult to define as either Fischer or Schrock carbenes.^{104,119}



The α -fluorine migration process (eq 9) may be fully reversible, as can be exemplified by the CF_3 analogue of Wilkinson's catalyst (eq 10). Both the trifluoromethyl complex and the difluorocarbene fluoride have been isolated and fully characterized, including single crystal X-ray diffraction.¹²⁰ Fluorine atoms in the α -position of a perfluoroalkyl on a metal center are susceptible to electrophilic attack by Brønsted and Lewis acids.¹⁰⁴ This chemistry is rich and has been recently reviewed.¹⁰⁶ Unlike free dihalocarbenes, which are not easily hydrolyzable, their metal complexes readily react with water to produce carbonyls.^{104,106} This reactivity has been used to develop a CO-free, Pd-catalyzed carbonylation reaction where the source of carbonyl was CCl_2 generated in situ from chloroform and alkali and hydrolyzed to CO upon coordination to Pd.¹²¹



3.2. Electronic Effects of CF_3 : Is It an Electron Acceptor or Donor?

Electronic properties of CF_3 as a ligand have been one of the most intriguing and controversial issues in the chemistry of trifluoromethyl metal complexes. In organic chemistry, the CF_3 group is conventionally viewed as an inductive electron acceptor.^{20,122} Indeed, the Hammett, Swain–Lupton (modified), and Taft electronic parameters for CF_3 are $\sigma_m = 0.43$, $F = 0.38$, and $\sigma_F = 0.46$, respectively.¹²² In accord with this, electrochemical data shows that benzonitrile is oxidized more reluctantly and reduced more easily than toluene and benzene.¹²³ A similar trend has been observed for a series of trifluoromethyl complexes and their methyl counterparts.^{124,125} Furthermore, Pt(II) has been shown to become less prone to oxidative addition upon replacement of methyls on the metal with CF_3 ligands,¹²⁶ although it is unknown to what degree steric effects of the much bulkier trifluoromethyl group contribute to the overall reactivity pattern (see below).

On the other hand, numerous observations point to considerable electron donation from CF_3 to the metal atom in trifluoromethyl complexes. The CF_3 ligand has been found to efficaciously stabilize derivatives of certain metals in high oxidation states.^{127–129} It has been widely recognized since the early 1970s¹³⁰ that the trans influence¹³¹ of CF_3 as a ligand is very strong, being

comparable to that of the methyl group.^{47,48,112,120,132–135} Examples of facile abstraction by Ag^+ of a halide trans to CF_3 in octahedral Ir^{111} , Ru^{111b} and $\text{Pt}^{130,136}$ complexes have been reported, pointing to the significant trans effect of the trifluoromethyl ligand. A convincing illustration of the strong structural trans influence of CF_3 is presented in Figure 1, displaying the superimposed molecules of $[(\text{dppe})\text{Pd}(\text{CF}_3)(\text{Cl})]$ and its nonfluorinated congener $[(\text{dppe})\text{Pd}(\text{CH}_3)(\text{Cl})]$.¹³⁵ The two show essentially identical coordination geometry around Pd, including the Pd–P bond distances trans to the CF_3 [2.345(1) Å] and to the CH_3 [2.339(1) Å] ligands. The recently reported¹²⁵ crystallographic data for $[(\text{BOXAM})\text{Ni}(\text{X})]$ (Scheme 3) show that the structural trans influence is virtually the same for $\text{X} = \text{CH}_3$, Ph , and CF_3 , as follows from the Ni–N bond distances trans to X: 1.933(3), 1.939(2), and 1.921(3) Å, respectively. As the trans influence is directly linked to ligand's ability to serve as a σ -donor,^{131,137–139} the CF_3 ligand appears to be a strong one. In full accord with this, computed natural atomic charges for $[(\text{H}_3\text{P})_3\text{Rh}(\text{CF}_3)]$ and $[(\text{H}_3\text{P})_3\text{Rh}(\text{CH}_3)]$ show (Scheme 4) that the Rh atom in the CF_3 species bears a large negative charge (−0.52) that even exceeds that for the methyl complex (−0.48).¹²⁰ This is in spite of the opposite, strong charges on the carbon atoms of the CF_3 (+0.79) and the CH_3 (−0.96) ligands. A similar trend was more recently observed for two pairs of Cr(V) and Cr(II) complexes bearing CH_3 and CF_3 ligands.¹⁴⁰ The extreme fluxionality of $[(\text{Ph}_3\text{P})_3\text{Rh}(\text{CF}_3)]$ in solution is convincingly linked to the powerful electron donation from the trifluoromethyl ligand to the metal in both the ground and transition states.¹²⁰

One might see a dichotomy in the two sets of data related to electronic properties of the trifluoromethyl group: indeed, some

observations point to its strong electron-withdrawing effect, whereas others imply powerful electron donation. Note that in both organic^{122,141} and metal CF_3 derivatives, π -effects are minor. Strong $\text{M}(\text{d}\pi) - \text{CF}_3(\sigma^*)$ interaction (back-donation) that was proposed in the early reports on the subject in the 1960s has not found support^{142–145} since its original MO analysis by Hall and Fenske.¹⁴⁶ Leyssens, Harvey, and co-workers¹⁴⁵ have recently estimated the π -acidity of the CF_3 ligand to be similar to that of pyridine and PR_3 ($\text{R} = \text{H}, \text{Me}, \text{Ph}$). Therefore, it is appropriate to consider mostly inductive (field) effects of the CF_3 group/ligand in a rationale for the apparent “contradiction” between the facts pointing to its either electron-withdrawing or electron-donating character.

A closer and broader look at the literature data, however, suggests that in fact there might be little contradiction, if any. As early as 1975, Holmes and Thomas¹⁴⁷ published a report entitled “Electron Distribution in Trifluoromethylbenzenes. Electron Donation by the Trifluoromethyl Group”. In that paper, core-electron ionization potentials were measured by ESCA for PhCF_3 , 1,3- $(\text{CF}_3)_2\text{C}_6\text{H}_4$, and 1,4- $(\text{CF}_3)_2\text{C}_6\text{H}_4$ to study the distribution of charge within these molecules. These distributions are shown in Scheme 5, indicating that while conferring electron-deficiency on the entire system, the CF_3 group serves as an *electron donor* to an adjacent carbon, in agreement with the even earlier reported theoretical calculations by Taft and Brownlee¹⁴⁸ and the π -inductive model used by Holtz.¹⁴¹ Confirmed by others,^{149–151} this charge distribution pattern

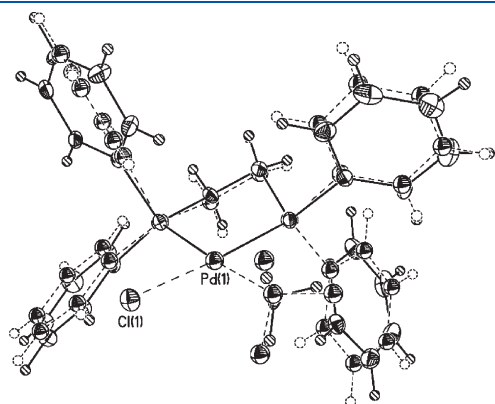
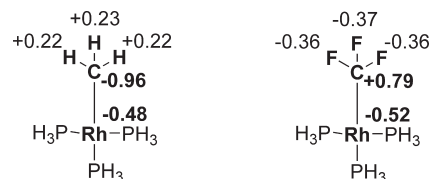
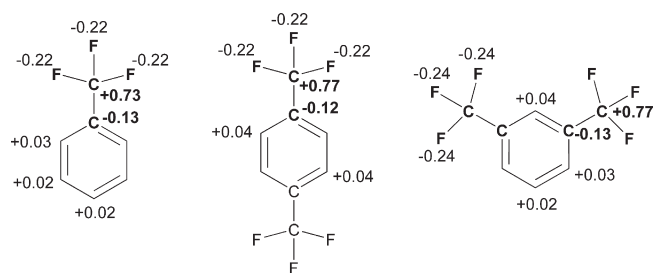


Figure 1. The superimposed molecules of $[(\text{dppe})\text{Pd}(\text{CF}_3)\text{Cl}]$ and $[(\text{dppe})\text{Pd}(\text{CH}_3)\text{Cl}]$, showing essentially identical coordination geometry around Pd.¹³⁵

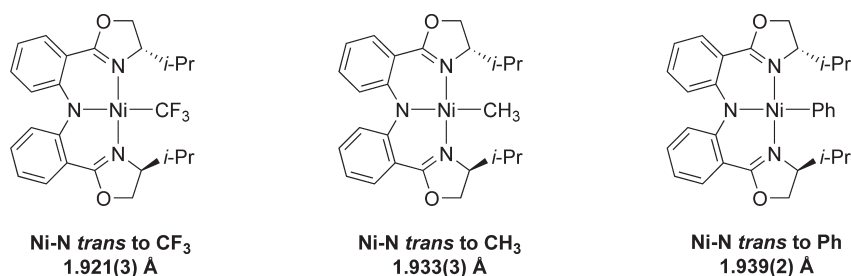
Scheme 4



Scheme 5



Scheme 3



represents a case of the general Pople–Gordon¹⁵² β -effect described as early as 1967: substitution of F for H on a carbon atom of an organic molecule *increases* the negative charge on the next C or H atom. The charges induced by this substitution alternate in a decaying manner, $F^{\delta-} \leftarrow C^{\delta+} \leftarrow C^{\delta\delta-} \leftarrow C^{\delta\delta+}$, etc., and hence for a CF_3 substituent this polarization $[F_3C] - C^{\delta\delta-} - C^{\delta\delta+}$ results in a dipole that reinforces the primary $F^{\delta-} C^{\delta+}$ moment.¹⁵² The Pople–Gordon model has received support for both trifluoromethylated aromatic (see above) and aliphatic^{153,154} compounds. For instance, the Mulliken and NAO negative charges on the carbon atom of the CH_3 group are considerably larger in CH_3CF_3 than in ethane.¹⁵⁴ The computed charges on the central carbon atom of propane,¹⁵⁵ $CF_3CH_2CH_3$,¹⁵⁶ and $CF_3CH_2CF_3$ are similar, which is in accord with the fact that $CF_3CH_2CF_3$ is not nearly as CH -acidic as CF_3CH_2CN .¹⁵⁷ Apparently, the β -effect might well take place in trifluoromethyl complexes of metals, as can be seen from the remarkably similar charge distribution trends shown in Schemes 4 and 5.

Considering the above, we propose that the seeming “dichotomy” of electronic properties of a CF_3 group/ligand emerges from an overlap of two effects. On replacement of a hydrogen atom or an alkyl group on a molecule with CF_3 , the three strongly electronegative fluorine atoms confer extra electron deficiency on the molecule *as a whole*. This certainly accords with the aforementioned electrochemical^{124,125} and ESCA¹⁴² data for $M-CF_3$ complexes and their $M-CH_3$ analogues. At the same time, the charges induced by this replacement of CF_3 for H or Alk on a carbon or a metal atom alternate, so that the atom adjacent to the CF_3 becomes more negatively (or less positively) charged.

Can our simple model, however, account for the aforementioned fact¹²⁶ that $Pt(II)$ becomes less reactive toward oxidative addition upon replacement of the methyls on the metal with CF_3 ligands? Apparently it can and it does. Simple electrostatic field considerations suggest that all d orbitals on the metal in a square planar complex L_3M-CX_3 should be more stabilized for $X = F$ than for $X = H$, because the carbon atom bonded to M bears a strong positive charge for $X = F$ but a negative charge for $X = H$. Indeed, this has been observed experimentally (ESCA) and confirmed computationally by Bancroft, Puddephatt, and co-workers¹⁴² for a series of $[L_2Pt(CF_3)_2]$ and analogous $[L_2Pt(CH_3)_2]$ complexes. While this should translate into diminished nucleophilicity of the metal centers for the CF_3 -ligated complexes, the replacement of the methyl with CF_3 does *not* necessarily result in more positive charge on Pt. According to the calculations,^{120,158} both $[(H_3P)_3Rh(CF_3)]$ and $[(H_3P)_3Rh(CH_3)]$ have a complete set of four occupied d-orbitals and the higher lying unoccupied $d(x^2-y^2)$. Pairwise comparison of each d orbital for the two molecules shows that in the CF_3 system the orbitals are 9–15 kcal mol⁻¹ (3000–5000 cm⁻¹) more stable than in the CH_3 analog. Yet, the charge on Rh in $[(H_3P)_3Rh(CF_3)]$ is *more negative* than in $[(H_3P)_3Rh(CH_3)]$ (Scheme 4), as determined in the same computational study. In other words, CF_3 makes the metal more negatively charged while bringing down in energy all of its d orbitals, thus making it less reactive toward oxidative addition reactions predominantly controlled by overlap of metal's HOMO with reagent's LUMO. As strange as an increase in the negative charge on an atom with simultaneous stabilization of its HOMO might look upon initial consideration, such phenomena are actually quite common in chemistry. A large negative charge on an atom is no guarantee for its high nucleophilicity: numerous inorganic anions such as SO_4^{2-} , NO_3^- , and PO_4^{3-} have strongly negatively charged oxygen atoms while being extremely poor nucleophiles. Another good example is numerous reactions of

bidentate nucleophiles such as CN^- , SCN^- , NO_2^- , various enolates, etc., which, in frontier orbital-controlled reactions, attack electrophiles not by the atom bearing the strongest negative charge but by the one having the highest orbital density (HOMO).¹⁵⁹ Interestingly, the sulfite ion SO_3^{2-} most often (albeit not always) attacks electrophiles with its sulfur despite the fact that the O atoms bear a strong negative charge and that the S atom is positively charged.¹⁶⁰

Steric factors might also be a significant contributor to the decrease of reactivity of $Pt(II)$ toward oxidative addition upon replacement of the methyls on the metal with CF_3 ligands. As has been known since the 1966 Chock–Halpern report,¹⁶¹ the rate of oxidative addition of CH_3I to $[(Ph_3P)_2Ir(CO)(X)]$ follows the order $X = Cl > Br > I$, in contrast with the reverse, “normal” order observed for the reactions of H_2 and O_2 with the same Vaska-type complexes. Being of S_N2 character, the CH_3I oxidative addition reaction appears to be more sensitive to the steric bulk rather than electronic properties of the halide on Ir. The difference in the van der Waals radii of Cl (1.75 Å), Br (1.85 Å), and I (1.98 Å)¹⁶² is much smaller than that of CH_3 (2.0 Å) and CF_3 (2.7 Å).⁴⁴ This suggests that steric effects should not be neglected when comparing reactivity of $M-CF_3$ complexes and their $M-CH_3$ counterparts toward oxidative addition reactions, at least those of S_N2 type.

Finally, another point that is worth making deals with the inverse relation between the trans influence of a ligand and its electronegativity.¹³⁸ The value of 3.5 cited¹⁴⁴ for the electronegativity of CF_3 on the Pauling scale is similar to that of oxygen. Others¹⁶³ have assigned to CF_3 electronegativities between that of fluorine (4.0) and that of chlorine (3.0). These numbers suggest that CF_3 should be a weak trans influence ligand. However, this is not the case as in fact the trans influence of CF_3 is very strong, being comparable to that of CH_3 and Ph (see above). Again, this contradiction is only seeming in the light of the above and of the recent work of Thomas, Gard, and co-workers.¹⁶⁴ Their ESCA studies show that the core ionization energies reflecting the effect of the CF_3 group on an adjacent atom and on a remote atom within the same molecule are different, which translates into different electronegativity values for CF_3 depending on which site of the molecule is probed. Thus, the group electronegativity for CF_3 has been shown¹⁶⁴ to be as low as that of bromine for a proximal atom, yet greater than that of fluorine for a more remote atom. (This is the opposite of the effect of fluorine whose effect is large on an adjacent atom but small on a distal atom.) It is also noteworthy that CF_3^- has been placed in the same category of “less electronegative ligands” as H^- .¹⁶⁵

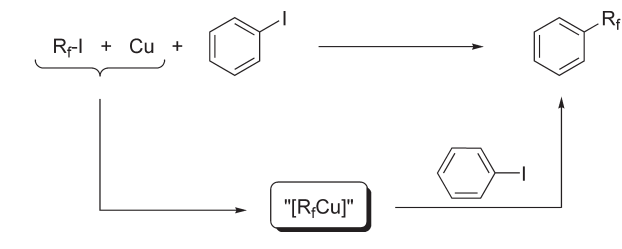
As follows from the above, the recent views of R_f groups as “hard” ligands with a marked electron-withdrawing ability¹²⁹ and of the CF_3 ligand exhibiting “extreme electron-withdrawing properties”¹²⁵ are somewhat far-fetched and may be misleading.

3.3. Copper

In their original article reporting perfluoroalkylation of haloarenes with perfluoroalkyl iodides in the presence of Cu metal (eq 1), McLoughlin and Thrower⁵⁶ presented solid evidence for $Cu-R_f$ intermediates in the reaction. They clearly demonstrated that the perfluoroalkylation can be carried out not only in one pot but also in two separate steps. It was shown that copper powder reacted with R_fI to produce an organocopper reagent. The latter was then heated with ArX to bring about the $Ar-R_f$ bond formation (Scheme 6).

The formation of the R_fCu reagents readily occurred in DMSO at 100–120 °C or in pyridine at 70–100 °C. The pregenerated solutions of perfluoroalkyl copper reagents were found to be air-sensitive yet quite stable to hydrolysis. For instance, addition of 5 equiv of water to the preformed “ $n-C_7F_{15}Cu$ ” in DMSO under

Scheme 6



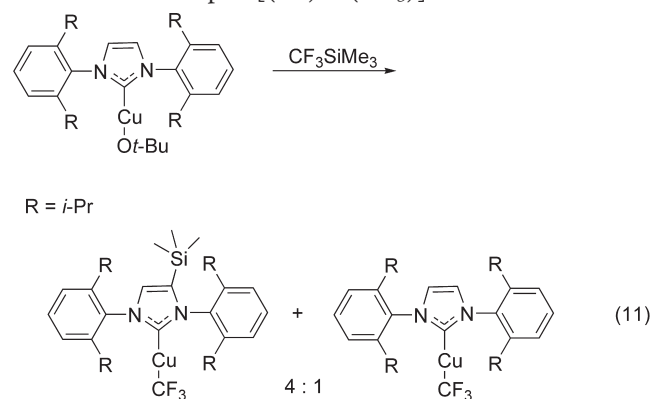
O_2 -free conditions resulted in sluggish hydrolysis to only 10–15% of $n-C_7F_{15}H$ after 3 days at room temperature. Furthermore, the perfluoroheptylcopper was isolated under argon by diluting its DMSO solution with water, followed by ether extraction, drying with $MgSO_4$, and evaporation. That produced a viscous oil which solidified on standing at ambient temperature and analyzed for Cu as $C_7F_{15}Cu \cdot OEt_2$. The compound was remarkably stable in DMSO or DMF in the absence of air, exhibiting no signs of decomposition and retaining its reactivity toward iodobenzene even after 3 months at room temperature. The R_fCu reagents were found to be much more thermally stable than conventional copper alkyls.

In 1980, Kondratenko, Vechirko, and Yagupolskii¹⁶⁶ described the formation of “ CF_3Cu ” from $(CF_3)_2Hg$ or CF_3HgI and Cu powder in NMP or DMAC. In 1985, CF_3 transfer from Zn or Cd to Cu was demonstrated for trifluoromethylation of iodobenzene in 80% yield.⁹⁵ However, it was not until 1986 that the first spectroscopic study of a copper perfluoroalkyl was reported by Wiemers and Burton.¹⁶⁷ They found that on treatment of $CuBr$ with CF_3CdX in DMF at $-50^\circ C$, a CF_3Cu species [A] was produced that resonated at -28.8 ppm in the ^{19}F NMR spectrum. After HMPA was added, no change in the spectral pattern was observed at $-50^\circ C$ or room temperature. However, when the solution was allowed to warm to room temperature in the absence of HMPA, two new CF_3Cu species, [B] and [C], were detected by ^{19}F NMR, displaying signals at -32.3 and -35.5 ppm, respectively. As these two peaks from [B] and [C] grew while the original one from [A] was diminishing in intensity, parallel formation of a CF_3CF_2Cu complex occurred, and after 11 h at room temperature the CF_3CF_2Cu compound was the only ^{19}F NMR-observable R_fCu species. It was concluded that in the absence of HMPA, the originally produced [A] is converted to [B] and [C] and eventually to [C], which then slowly decomposed to the C_2F_5Cu derivative. The latter is likely formed via α -F-elimination, leading to difluorocarbene, which then inserts into the $Cu-CF_3$ bond. The three complexes [A], [B], and [C] exhibited markedly different reactivity toward hydrolysis, air-oxidation, and trifluoromethylation of organic halides. Later on, the ^{19}F NMR signals from [A], [B], and [C] were assigned to $[(CF_3)Cu] \cdot L$ (L = “metal halide”), $[(CF_3)_2Cu]^-$, and $[Cu(CF_3)_4]^-$.^{127,168} However, detailed structural information on [A], [B], and [C] could not be obtained, and it is not surprising that Wiemers and Burton themselves identified the thus generated trifluoromethylcopper as an “elusive and complex species”.¹⁶⁷ More recently, Kolomeitsev and co-workers¹⁶⁸ reported that a spectroscopically similar CF_3Cu reagent can be efficiently prepared from CF_3SiMe_3 , $CuBr$, and KF in DMF–DMI at $0^\circ C$. They have proposed that the three ^{19}F NMR-observable CF_3Cu species in this system are $[(CF_3)Cu] \cdot KBr$ (-28.8 ppm), $K[(CF_3)_2Cu]$ (-32.4 ppm), and $K[Cu(CF_3)_4]$ (-35.7 ppm). The latter, a

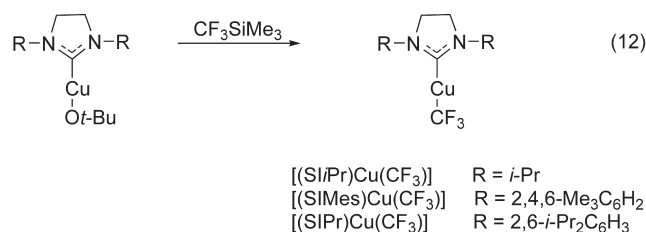
$Cu(III)$ species, has been shown to remain the only trifluoromethyl Cu complex in the mixture after its exposure to dry air for 2 days.¹⁶⁸ Most recently, similar ^{19}F NMR patterns were reported for solutions of “ CF_3Cu ” obtained upon treatment of $CuBr$ with $Zn(CF_3)Br \cdot 2DMF$ in DMF.¹¹⁴ The signals at -32.0 , -28.4 , and -35.1 ppm were assigned to $CuCF_3$, $Cu[Cu(CF_3)_2]$, and $Cu[Cu(CF_3)_4]$, respectively. It is noteworthy that the assignments of the ^{19}F NMR signals observed by all three groups^{114,127,168} are still tentative because unambiguous structural information on these species remains nonexistent. Note that ^{19}F NMR chemical shifts of -33.2 and -31.5 ppm have been reported for structurally characterized $PPN^+ [Cu(CF_3)_4]^-$ and $[(SiMe)_2Cu]^+ [Cu(CF_3)_2]^-$, respectively (see below).

The first reported structurally characterized $CuCF_3$ species were $Cu(III)$ complexes.^{127,128a} Oxidation of a compound formulated as $[CdI]^+ [Cu(CF_3)_2]^-$ with thiuramdisulfide produced $[(Et_2NCS_2)Cu(CF_3)_2]$.¹²⁷ A striking structural feature of this compound is the vastly different $Cu-CF_3$ bond distances, 1.863(5) and 2.026(5) Å. A series of remarkably stable salts $X^+ [Cu(CF_3)_4]^-$ have been prepared by oxidation of $CuCF_3$ in DMF with various oxidants such as XeF_2 , I_2 , Br_2 , Cl_2 , or ICl .^{128a} The products have been reliably characterized, including X-ray diffraction for $X = PPN$ [$Cu-CF_3 = 1.967(6)$ Å]. On treatment of $[(Ph_3P)_3Cu(OR)]$ [$R = Ph, CH(CF_3)_2$] with Ruppert’s reagent $[(Ph_3P)_3Cu(CF_3)]$ was produced, isolated in 30–92% yield, and characterized by NMR, IR, and elemental analysis.¹⁶⁹

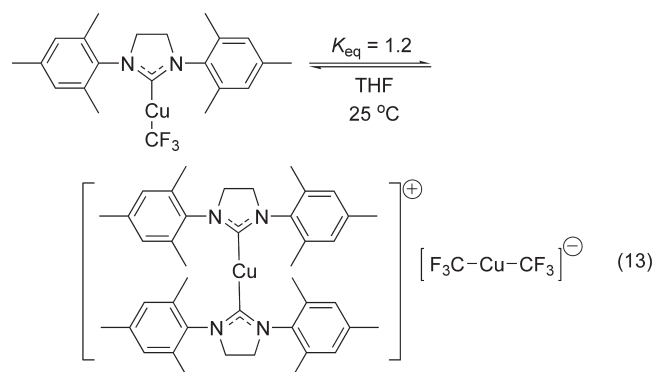
Vicic and co-workers⁶⁰ have reported the first fully characterized $Cu(I)$ trifluoromethyl complexes. Surprisingly, the treatment of $[(iPr)Cu(OBu-t)]$ with Ruppert’s reagent gave rise to a ca. 1:4 mixture of the expected product $[(iPr)Cu(CF_3)]$ and its analog bearing a $SiMe_3$ group on the NHC ring (eq 11). The “anomalous” product was isolated and fully characterized, including X-ray analysis. The $Cu-CF_3$ bond distance in this complex [1.967(6) Å] is ca. 0.05 Å longer than that in a similar nonfluorinated complex $[(iPr)Cu(CH_3)]$.



To avoid the silylation of the imidazolium ring (eq 11) Vicic et al. then prepared saturated NHC-stabilized $Cu-CF_3$ complexes $[(SiPr)Cu(CF_3)]$,⁶⁰ $[(SiMe)_2Cu(CF_3)]$,¹⁷⁰ and $[(SiPr)Cu(CF_3)]$ ¹²⁵ from the corresponding $t-BuOCu$ derivatives and CF_3SiMe_3 (eq 12). The starting $t-BuOCu$ complexes were monomeric for $NHC = SiMe$ and $SiPr$, whereas the $SiPr$ alkoxide was a dimer. All these $CuCF_3$ derivatives have been characterized, including a single crystal diffraction study of $[(SiPr)Cu(CF_3)]$ ⁶⁰ and an electrochemical study of $[(SiPr)Cu(CF_3)]$.¹²⁵



While $[(\text{Si}i\text{Pr})\text{Cu}(\text{CF}_3)]$ and $[(\text{Si}i\text{Pr})\text{Cu}(\text{CF}_3)]$ retain their structures in solution, $[(\text{SiMe}_3)\text{Cu}(\text{CF}_3)]$ has been found¹⁷⁰ to slowly (ca. 100 h at 25 °C) equilibrate with the corresponding cuprate $[(\text{SiMe}_3)_2\text{Cu}]^+ [\text{Cu}(\text{CF}_3)_2]^-$ (eq 13) that has been structurally characterized. Again, the Cu–C bond distance in the anion $[\text{Cu}(\text{CF}_3)_2]^-$ [1.970(6) Å] is slightly (0.02–0.05 Å) longer than in $[\text{Cu}(\text{CH}_3)_2]^-$.¹⁷⁰ The ^{19}F NMR chemical shift of the signal from $[(\text{SiMe}_3)_2\text{Cu}]^+ [\text{Cu}(\text{CF}_3)_2]^-$ (–31.5 ppm) is close to those (–32.3 and –32.4 ppm) assigned by others^{127,167,168} to $[\text{Cu}(\text{CF}_3)_2]^-$ spontaneously generated from “ligandless” CuCF_3 (see above). Trifluoromethylation reactions with well-defined NHC Cu(I) trifluoromethyl complexes are discussed in section 4.1.5 below.



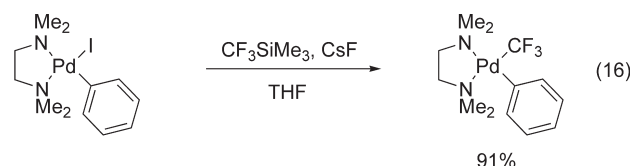
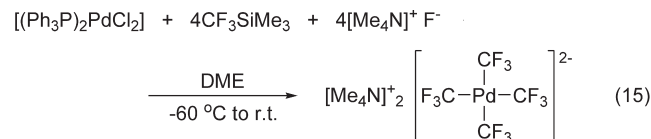
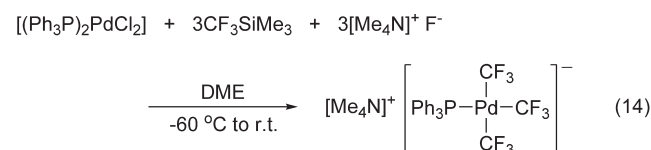
3.4. Palladium

The first perfluoroalkyl palladium complexes were reported by Stone, Maitlis, and Rosevear^{171,172} as early as the 1960s. They prepared $[(\text{bpy})\text{Pd}(\text{CH}_3)(n\text{-C}_3\text{F}_7)]$,¹⁷¹ $[(\text{bpy})\text{Pd}(n\text{-C}_3\text{F}_7)_2]$,¹⁷¹ $[(\text{Ph}_3\text{P})_2\text{Pd}(\text{CF}_3)(\text{I})]$,¹⁷² and $[(\text{dppe})\text{Pd}(\text{CF}_3)(\text{I})]$ ¹⁷² using oxidative addition reactions of the corresponding perfluoroalkyl iodides. For instance, passing CF_3I through a solution of $[(\text{Ph}_3\text{P})_4\text{Pd}]$ produced $[(\text{Ph}_3\text{P})_2\text{Pd}(\text{CF}_3)(\text{I})]$ in 78% yield. Some $\text{R}_f\text{-Pd}$ species have been obtained by Klabunde's¹⁰⁸ metal atom condensation with perfluoroalkyl halides and by Lagow's¹⁰⁹ method employing CF_3 radicals generated from the glow discharge of C_2F_6 (see section 3.1 above). Both methods require special equipment that is not common in a conventional organometallic chemistry laboratory. Krause and Morrison^{113b} have reported the formation of $[(\text{Et}_3\text{P})_2\text{Pd}(\text{CF}_3)(\text{Br})]$ and $[(\text{Et}_3\text{P})_2\text{Pd}(\text{CF}_3)_2]$ from $[(\text{Et}_3\text{P})_2\text{Pd}(\text{Br})_2]$ and $(\text{CF}_3)_2\text{Cd} \cdot \text{DME}$. Oxidative trifluoromethylation of $[(\text{Ph}_3\text{P})_4\text{Pd}]$ with $(\text{CF}_3)_2\text{TiOAc}$ has been mentioned^{113c} to give 5% of $[(\text{Ph}_3\text{P})_2\text{Pd}(\text{CF}_3)_2]$, whereas the reaction of $[(\text{Et}_3\text{P})_2\text{Pd}(\text{Cl})_2]$ with CF_3PbPh_3 afforded $[(\text{Et}_3\text{P})_2\text{Pd}(\text{CF}_3)(\text{Cl})]$ in 62% yield.^{113d}

Hughes et al.^{112,134} have prepared a series of complexes of the type $[(\text{tmeda})\text{Pd}(\text{CH}_3)(\text{R}_f)]$, where $\text{R}_f = \text{C}_2\text{F}_5$, $n\text{-C}_3\text{F}_7$, $i\text{-C}_3\text{F}_7$, $n\text{-C}_4\text{F}_9$, as shown in eq 4. These complexes were thoroughly characterized in solution and in the solid state. Jordan and co-

workers¹⁷³ have found that $[(\text{tmeda})\text{Pd}(\text{CH}_3)(n\text{-C}_3\text{F}_7)]$ reacts with dppp to give $[(\text{dppp})\text{Pd}(\text{CH}_3)(n\text{-C}_3\text{F}_7)]$, which then can be converted to $[(\text{dppp})\text{Pd}(\text{NMePh}_2)(n\text{-C}_3\text{F}_7)]^+ [\text{B}(\text{C}_6\text{F}_5)_4]^-$ on treatment with $[\text{HNMePh}_2]^+ [\text{B}(\text{C}_6\text{F}_5)_4]^-$. This cationic complex does not react with ethylene or vinyl chloride but is readily converted to $[(\text{dppp})\text{Pd}(\text{CO})(n\text{-C}_3\text{F}_7)]^+ [\text{B}(\text{C}_6\text{F}_5)_4]^-$ when exposed to CO.

In 2004, Naumann's group¹⁷⁴ reported a remarkable observation that is particularly important for the chemistry of trifluoromethylpalladium complexes in general and for Pd-catalyzed trifluoromethylation with Ruppert-type reagents in particular. It was found that on treatment of $[(\text{Ph}_3\text{P})_2\text{MCl}_2]$ ($\text{M} = \text{Pd}, \text{Pt}$) with CF_3SiMe_3 in the presence of $[\text{Me}_4\text{N}]^+\text{F}^-$, the generated CF_3^- carbanion equivalent can easily displace not only the chloro ligands but also the phosphines on the metal (eqs 14 and 15).¹⁷⁴ Nonselective displacement of halide and phosphine ligands with CF_3^- has also been observed^{59,135} for Pd aryls stabilized by monodentate and weakly bound bidentate phosphines. However, tightly binding diamino and diphosphino ligands on Pd are sufficiently resistant to this type of substitution by CF_3^- , which has allowed for the preparation of a large series of well-defined trifluoromethyl Pd complexes (e.g., eq 16),¹³⁵ usually in good to high yield (Table 1).^{66,135,175,176}



The problem of displacement of weakly bound phosphine ligands on Pd with CF_3^- deals with its facile uncontrolled release from $\text{CF}_3\text{SiMe}_3/\text{F}^-$. To obviate this problem, the desired trifluoromethylation can be performed on a Pd–F starting material with Ruppert's reagent in the absence of an external activator such as F^- . This way $[(\text{Ph}_3\text{P})_2\text{Pd}(\text{Ph})(\text{CF}_3)]$ and $[(\text{Xantphos})\text{Pd}(\text{Ph})(\text{CF}_3)]$ have been prepared in high yield (eq 17) and fully characterized, including X-ray diffraction.^{59,66} The corresponding Pd fluorides may be preisolated or used in situ. Interestingly, although both $[(\text{Ph}_3\text{P})_2\text{Pd}(\text{Ph})(\text{F})]$ ¹⁷⁷ and $[(\text{Ph}_3\text{P})_2\text{Pd}(\text{Ph})(\text{CF}_3)]$ ⁵⁹ are trans and $[(\text{Xantphos})\text{Pd}(\text{Ph})(\text{F})]$ is also trans, $[(\text{Xantphos})\text{Pd}(\text{Ph})(\text{CF}_3)]$ is cis in the solid state and predominantly cis in solution.⁵⁹ Most recently, Buchwald and co-workers⁶³ reported the synthesis of trifluoromethyl Pd(II) aryls stabilized by BrettPhos (eq 18). We propose that the modest yields of 37–38% are because of partial displacement of the BrettPhos ligand with CF_3^- . The X-ray structure of $[(\text{BrettPhos})\text{Pd}(4\text{-MeOC}_6\text{H}_4)(\text{CF}_3)]$ is

Table 1. Trifluoromethyl Complexes of Pd(II) Prepared with Ruppert's Reagent, Optionally Followed by Ligand Exchange

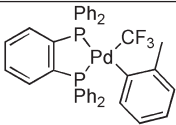
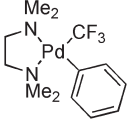
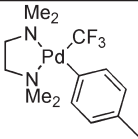
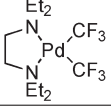
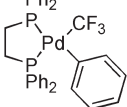
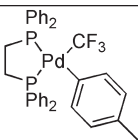
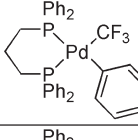
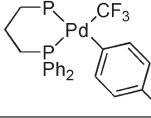
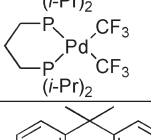
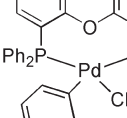
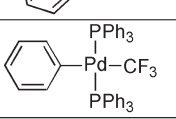
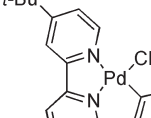

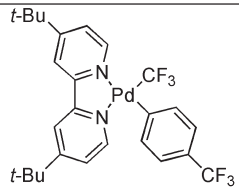
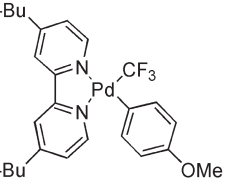
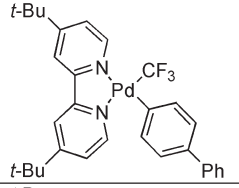
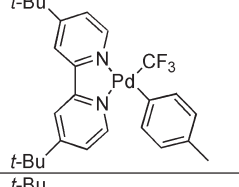
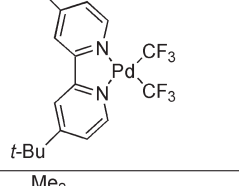
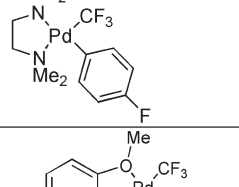
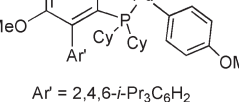
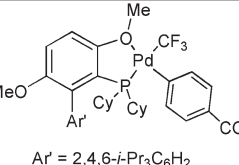
Trifluoromethyl Complex	Method of preparation	Yield, %	Characterization (EA = elemental analysis)	Ref
	$[(\text{dppbz})\text{Pd}(2\text{-Tol})(\text{Br})] + \text{CF}_3\text{SiMe}_3 + [\text{Bu}_4\text{N}]^+ [\text{Ph}_3\text{SiF}_2]^-$	52	X-ray, NMR, EA	175
	$[(\text{tmeda})\text{Pd}(\text{Ph})(\text{I})] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	91	X-ray, NMR, EA	135
	$[(\text{tmeda})\text{Pd}(4\text{-Tol})(\text{I})] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	90	NMR, EA	135
	$[(\text{teeda})\text{Pd}(\text{Cl})_2] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	59	X-ray, NMR, EA	135
	$[(\text{dppe})\text{Pd}(\text{Ph})(\text{I})] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	69	X-ray, NMR, EA	135
	$[(\text{tmeda})\text{Pd}(\text{Ph})(\text{CF}_3)] + \text{dppe} + \text{KHSO}_4$	85		
	$[(\text{tmeda})\text{Pd}(4\text{-Tol})(\text{CF}_3)] + \text{dppe} + \text{KHSO}_4$	96	NMR, EA	135
	$[(\text{tmeda})\text{Pd}(\text{Ph})(\text{I})] + \text{dppp} + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	71	X-ray, NMR, EA	135
	$[(\text{tmeda})\text{Pd}(4\text{-Tol})(\text{CF}_3)] + \text{dppp} + \text{KHSO}_4$	87	NMR, EA	135
	$[(\text{dipp})\text{Pd}(\text{Cl})_2] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	85	X-ray, NMR, EA	135
	$[(\text{Xantphos})\text{Pd}(\text{Ph})(\text{F})] + \text{CF}_3\text{SiMe}_3$	88	X-ray, NMR, EA	59
	$[(\text{Ph}_3\text{P})_2\text{Pd}(\text{Ph})(\text{F})] + \text{CF}_3\text{SiMe}_3$	82	X-ray, NMR, EA	59
	$[(t\text{-Bu-bpy})\text{Pd}(4\text{-C}_6\text{H}_4\text{F})(\text{I})] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	70	NMR, EA	176

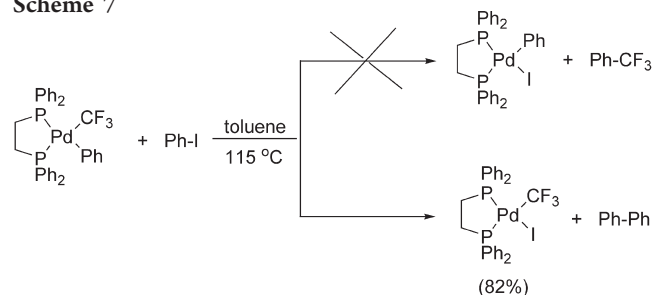
Table 1. Continued

Trifluoromethyl Complex	Method of preparation	Yield, %	Characterization (EA = elemental analysis)	Ref
	$[(t\text{-Bu-bpy})\text{Pd}(4\text{-C}_6\text{H}_4\text{CF}_3)(\text{I})] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	63	NMR, EA	176
	$[(t\text{-Bu-bpy})\text{Pd}(4\text{-C}_6\text{H}_4\text{OMe})(\text{I})] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	32	NMR, EA	176
	$[(t\text{-Bu-bpy})\text{Pd}(4\text{-C}_6\text{H}_4\text{Ph})(\text{I})] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	58	NMR, EA	176
	$[(t\text{-Bu-bpy})\text{Pd}(4\text{-Tol})(\text{I})] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	49	NMR, EA	176
	$[(t\text{-Bu-bpy})\text{Pd}(\text{Cl})_2] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	61	NMR, EA	176
	$[(\text{tmeda})\text{Pd}(4\text{-C}_6\text{H}_4\text{F})(\text{I})] + \text{CF}_3\text{SiMe}_3 + \text{CsF}$	76	NMR, EA	176
 Ar' = 2,4,6- <i>i</i> -Pr ₃ C ₆ H ₂	$[(\text{BrettPhos})\text{Pd}(4\text{-C}_6\text{H}_4\text{OMe})(\text{Cl})] + \text{CF}_3\text{SiEt}_3 + \text{CsF}$	37	X-ray, NMR	63
 Ar' = 2,4,6- <i>i</i> -Pr ₃ C ₆ H ₂	$[(\text{BrettPhos})\text{Pd}(4\text{-C}_6\text{H}_4\text{CO}_2\text{Me})(\text{Cl})] + \text{CF}_3\text{SiEt}_3 + \text{CsF}$	38	X-ray, NMR	63

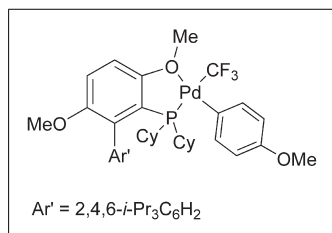
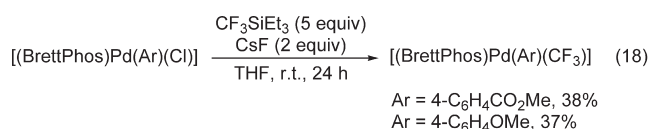
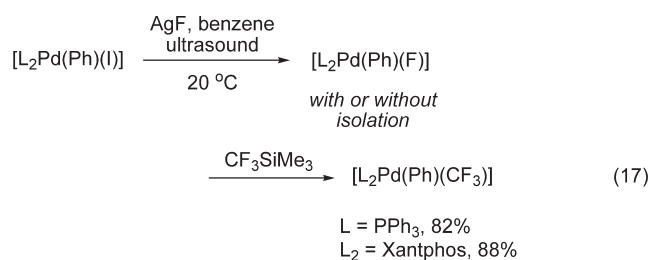
remarkable in that the Pd atom is chelated by the P center and the methoxy group in its vicinity, as shown in eq 18. Also very recently, a few $\text{CF}_3\text{Pd}(\text{IV})$ complexes were reported.^{176,178} The reaction of $[(t\text{-Bu-bpy})\text{Pd}(4\text{-C}_6\text{H}_4\text{F})(\text{CF}_3)]$ with *N*-fluoro-2,4,6-trimethylpyridinium triflate produced octahedral $[(t\text{-Bu-bpy})\text{Pd}(\text{CF}_3)(\text{F})(\text{OTf})(\text{C}_6\text{H}_4\text{F})]$ that was isolated in 53% yield and

structurally characterized.¹⁷⁶ Another $\text{CF}_3\text{Pd}(\text{IV})$ complex, $[(\text{bzq})\text{Pd}(\text{CF}_3)(\text{OAc})_2(\text{OH}_2)]$, has been prepared in 2–65% yield via electrophilic trifluoromethylation of $[(\text{bzq})\text{Pd}(\text{OAc})]$ dimer with 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole, 1,3,3-tris-(trifluoromethyl)-1,2-benziodoxole, 1-(trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one, or 5-(trifluoromethyl)dibenzothiothiophenium triflate

Scheme 7

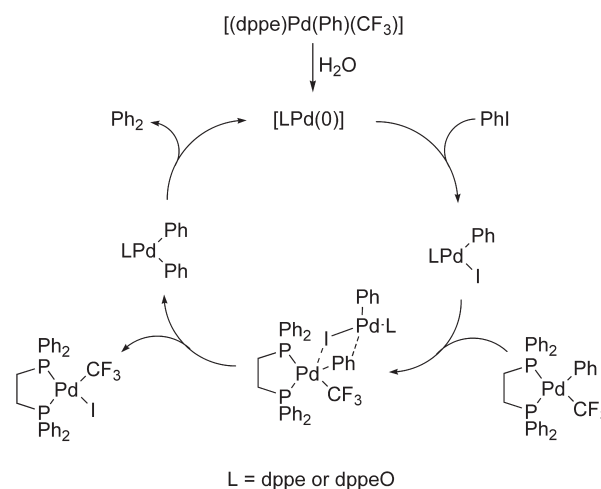


or tetrafluoroborate.¹⁷⁸ The structure of $[(\text{bzq})\text{Pd}(\text{CF}_3)(\text{OAc})_2(\text{OH}_2)]$ has been determined by X-ray diffraction.



All recently prepared trifluoromethyl Pd aryls have been made in order to study $\text{Ar}-\text{CF}_3$ reductive elimination, a highly sought after process required for Pd-catalyzed trifluoromethylation of haloarenes, as described in sections 4.2 and 5. During the quest for $\text{Ar}-\text{CF}_3$ bond formation at Pd, however, some interesting transformations have been found that are worth mentioning. The thermal decomposition of $[(\text{dppe})\text{Pd}(\text{Ph})(\text{CF}_3)]$ in the presence of PhX ($\text{X} = \text{I}, \text{Cl}$) was originally hoped to produce PhCF_3 along with $[(\text{dppe})\text{Pd}]$ to be trapped by PhX oxidative addition, leading to $[(\text{dppe})\text{Pd}(\text{Ph})(\text{X})]$.¹³⁵ A totally unexpected reaction occurred instead, giving rise to $[(\text{dppe})\text{Pd}(\text{CF}_3)(\text{X})]$ and Ph_2 (Scheme 7). A thorough study of this striking transformation showed that it was catalyzed by minute quantities of adventitious water. The mechanism of catalysis is remarkable, involving H_2O -induced reduction of a small quantity of the initial Pd(II) complex to Pd(0) . Two routes from $[(\text{dppe})\text{Pd}(\text{Ph})(\text{CF}_3)]$ and H_2O to Pd(0) have been identified and studied in detail.¹³⁵ One is initiated by $\alpha\text{-F}$ -elimination followed by hydrolysis of the resultant difluorocarbene to carbonyl, migratory insertion, and reductive elimination of PhC(X)O , where $\text{X} = \text{F}, \text{OH}$, or OOCPh . The other pathway involves the $\text{Pd(II)}/\text{P(III)}$ to $\text{Pd(0)}/\text{P(V)}$ redox process,¹⁷⁹ leading to dppeO , Pd(0) , and CHF_3 .¹³⁵ As shown in Scheme 8, the Pd(0) produced these ways oxidatively adds PhX to give a $\sigma\text{-Ph}-\text{Pd(II)}$ species. The latter then undergoes transmetalation with $[(\text{dppe})\text{Pd}(\text{Ph})(\text{CF}_3)]$, followed

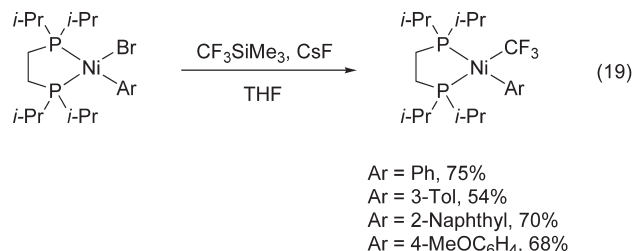
Scheme 8



by $\text{Ph}-\text{Ph}$ reductive elimination, leading to the final products and regenerating Pd(0) .

3.5. Nickel

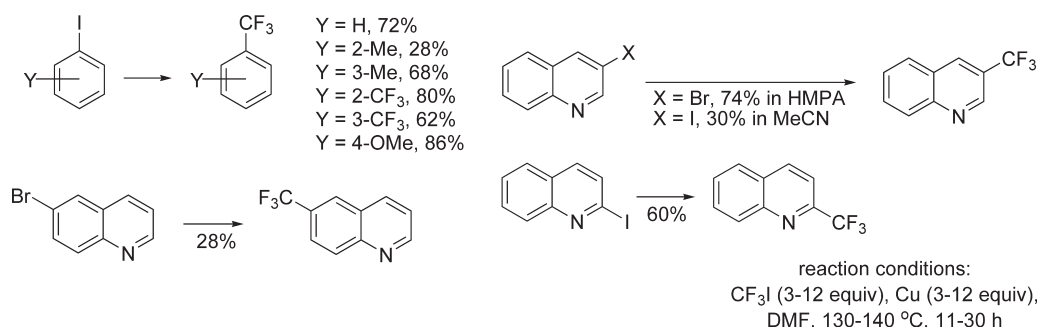
The first perfluoroalkyl complexes of Ni were synthesized by Stone's group in the 1960s.^{180–182} The early methods were based on oxidative addition of perfluoroalkyl iodides to Ni complexes,^{180–185} e.g., the formation of $[\text{LNi}(\text{R}_f)(\text{L}')]$ (where $\text{L} = \text{dppe}$, $\text{L}' = \text{I}$, $\text{R}_f = \text{C}_2\text{F}_5$, $n\text{-C}_3\text{F}_7$,¹⁸⁰ $\text{L} = \text{Cp}$, $\text{L}' = \text{CO}$, $\text{R}_f = \text{CF}_3$, C_2F_5 , $n\text{-C}_3\text{F}_7$ ¹⁸¹) upon treatment of $[(\text{dppe})\text{Ni}(\text{CO})_2]$ or $[\text{CpNiCO}]_2$ with the corresponding R_fI . Nickel perfluoroalkyls have been proposed¹⁸⁶ as products of the reaction of $[\text{Ni}(\text{CO})_4]$ with R_fI in donor solvents. The first structural characterization of a Ni perfluoroalkyl, $[\text{CpNi}(\text{PPh}_3)(\text{CF}_3)]$, was reported in 1970.¹⁸⁷ A series of trifluoromethyl nickel aryls $[(\text{dppe})\text{Ni}(\text{Ar})(\text{CF}_3)]$ has been recently prepared by Vicic (eq 19)¹⁸⁸ using the methodology previously developed for the synthesis of similar Pd complexes (cf. eq 16).¹³⁵ Double trifluoromethylation of $[(\text{dppe})\text{Ni}(\text{I})_2]$ with $\text{CF}_3\text{SiMe}_3/\text{CsF}$ afforded $[(\text{dppe})\text{Ni}(\text{CF}_3)_2]$ in 26% yield.¹⁸⁸ Two of the complexes, $[(\text{dppe})\text{Ni}(2\text{-naphthyl})(\text{CF}_3)]$ and $[(\text{dppe})\text{Ni}(\text{CF}_3)_2]$, have been structurally characterized. The structure of the latter revealed that the $\text{Ni}-\text{C}$ bond distances were similar, whereas $\text{Ni}-\text{P}$ bonds were longer than those previously determined for the nonfluorinated analogue $[(\text{dppe})\text{Ni}(\text{CH}_3)_2]$.



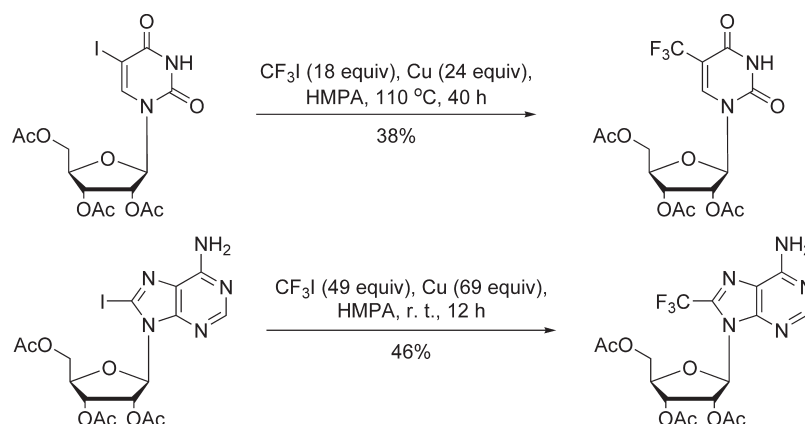
4. STOICHIOMETRIC $\text{Ar}-\text{CF}_3$ BOND FORMATION WITH METALS

The vast majority of metal-promoted aromatic trifluoromethylation reactions employ copper (section 4.1). Only in the last 5 years have the first examples of aromatic $\text{C}-\text{CF}_3$ bond formation at Pd and Ni centers been reported. These transformations are reviewed in section 4.2. Catalytic trifluoromethylation of aromatic compounds is described in section 5.

Scheme 9



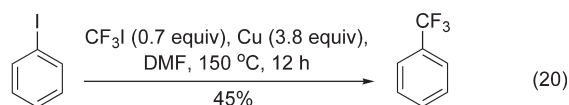
Scheme 10



4.1. Copper-Promoted Reactions

All existing methods for Cu-promoted aromatic trifluoromethylation can be divided into five groups by the nature of CF₃ source: (i) polyfluorinated methanes (CF₃I, CF₃Br, CF₂Br₂, CF₃H, etc.); (ii) derivatives of trifluoroacetic and fluorosulfonyldifluoroacetic acids; (iii) CF₃Cu species generated from trifluoromethyl derivatives of Hg(II), Zn(II), and Cd(II) via metathesis; (iv) Ruppert's reagent CF₃SiMe₃ and its ethyl analogue CF₃SiEt₃; and (v) well-defined trifluoromethyl copper complexes. Excellent reviews by Burton and Yang⁴⁵ and by McClinton and McClinton,⁴⁴ both published in 1992, provide an exhaustive description of methods (i)–(iv) up to the early 1990s. In this section, we present a general overview that covers both earlier publications and most recent reports on the subject. All copper-promoted trifluoromethylation reactions of iodo-, bromo-, and chloroarenes are summarized in Tables 2, 3, and 4, respectively.

4.1.1. Polyfluorinated Methanes as CF₃ Sources. In their pioneering work of the 1960s, McLoughlin and Thrower^{55,56} found that perfluoroalkyl-substituted aromatic compounds can be prepared directly from iodo-perfluoroalkanes and iodoarenes in the presence of copper powder (eq 1). Although their work was mostly focused on higher perfluoroalkyl iodides (see section 6) and only one example of trifluoromethylation was reported (eq 20), the new method was thoroughly investigated to become key for further developments in the area.

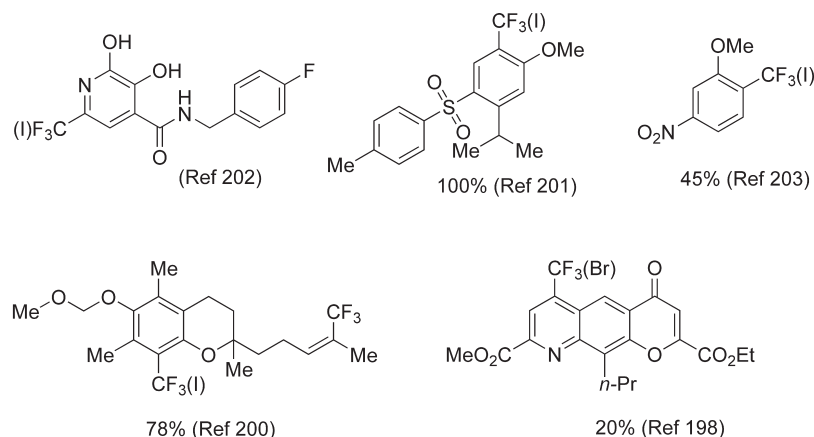


As described in section 3.3 above, it was shown that R_fCu reactive species are produced on treatment of R_fI with Cu powder and that these species can then react with haloarene substrates to give the corresponding perfluoroalkylarenes. Of many other metals screened, only copper promoted the coupling. Both DMSO and DMF were found to be the best solvents for the reaction, although pyridine, HMPA and DMAC could be used as successfully. The reaction required temperatures up to 150 °C, up to 4-fold excess of Cu metal, and up to 2-fold excess of iodoarene substrate.

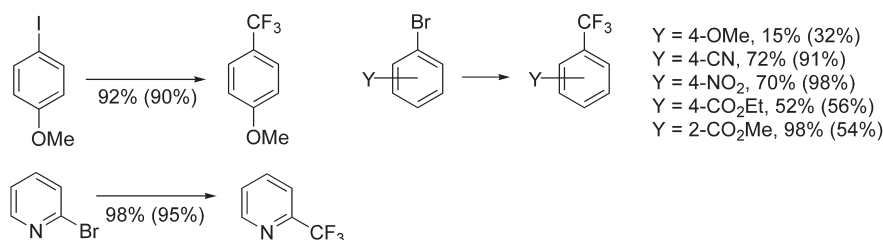
Following the original McLoughlin–Thrower patent publication⁵⁵ Kobayashi and Kumadaki⁵⁷ improved the trifluoromethylation reaction. The best yields were obtained in DMF with a 3–12-fold excess of both CF₃I and Cu powder that had been freshly precipitated from an aqueous solution of copper sulfate with zinc dust. The reaction proceeded at 130–140 °C for 11–20 h.^{57,189} As expected, aryl bromides and especially chlorides were much less reactive: PhBr gave rise to PhCF₃ in only 11% yield, whereas PhCl did not react at all. However, more electron-deficient 1-chloro-4-nitrobenzene as well as chloro- and bromo-substituted quinolines and isoquinolines did undergo trifluoromethylation under such conditions to furnish the desired products in 11–74% yield (Scheme 9).

Kobayashi et al. have also developed trifluoromethylation of simple heteroaromatic systems such as halopyrimidines¹⁹⁰ and more complicated substrates, halopyrimidine and halopurine nucleosides (Scheme 10).^{190,191} Rather electron-rich 2- and 3-bromobenzofurans were trifluoromethylated in 53–60% yield,¹⁹² although since then it has been found¹⁹³ that these reactions are not regioselective, giving rise to mixtures of isomers, especially when performed in pyridine.

Scheme 11



Scheme 12



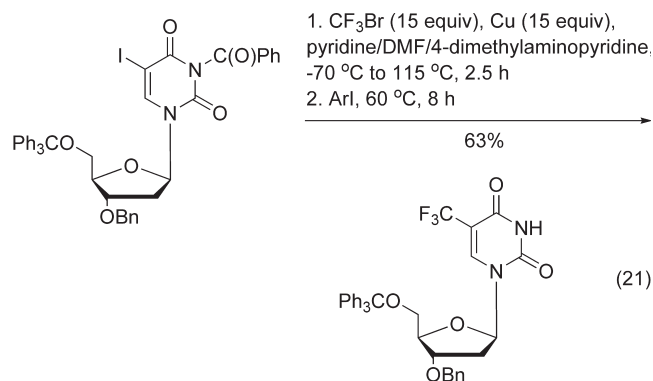
GC yields for: Protocol I (Protocol II)

Protocol I: a) Copper anode, CF_3Br (bubbling), $n\text{Bu}_3\text{P}$ (2 equiv), Bu_4NBr (0.05 equiv), Current 0.3 A, DMF, -15°C , 6 h; b) ArI, 90°C , 3 h.

Protocol II: Copper anode, ArI, CF_3Br (3 bar), tmeda (4 equiv), Bu_4NBr (0.05 equiv), Current 0.3 A, DMF, r. t., 20 min, then CF_3Br (3–6 bar), 95°C , 2 h.

The McLoughlin–Thrower reaction has been widely used for the synthesis of trifluoromethylated building blocks and compounds of particular interest, of which some are shown in Scheme 11.^{194–203} In this and some other schemes, a halogen atom in parentheses next to the CF_3 groups indicates if the trifluoromethylation was carried out using the corresponding iodo, bromo, or chloro starting material.

As CF_3I is expensive, a number of attempts have been made to replace it with a lower cost reagent. Kobayashi and Kumadaki²⁰⁴ observed considerably lower yields for trifluoromethylation of iodobenzene (22%) and 3-bromoquinoline (11%) upon replacement of CF_3I with CF_3Br under the same conditions. It

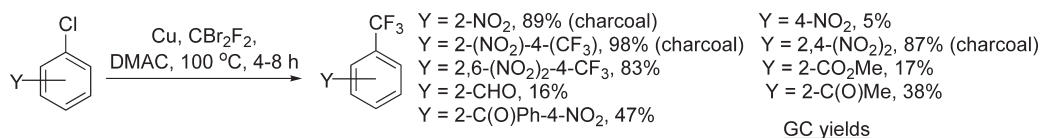


has been reported²⁰⁵ that solutions of “ligandless” CuCF_3 can be efficiently produced from CF_3Br and Cu in pyridine/DMF/4-(dimethylamino)pyridine and subsequently used (eq 21).

Another approach involves use of CF_3Br in an electrolytic cell with a copper anode (Scheme 12).²⁰⁶ Two procedures have been developed. In one (protocol I in Scheme 12), a CF_3Cu compound is pregenerated by bubbling CF_3Br through the cell containing a DMF solution of Bu_4NBr as supporting electrolyte and PPh_3 . The latter was added to avoid precipitation of the CuBr byproduct. After passing constant current through that mixture for 6 h, the substrate was then added to undergo trifluoromethylation. The second, more convenient procedure (protocol II in Scheme 12) employed an autoclave that was charged with all reagents. In protocol II, better yields were obtained when tmeda was used in place of PPh_3 . The two methods gave comparable yields that were high for iodoarenes, good to high for electron-deficient bromoarenes, and poor for electron-enriched bromoarenes (Scheme 12).

Highly electron-deficient aryl chlorides have been trifluoromethylated with $\text{Cu}/\text{CF}_2\text{Br}_2$ in DMAC (Scheme 13).^{207,208} The method is only applicable to chloroarenes bearing the most powerful electron-withdrawing groups. In some cases,²⁰⁸ better yields were obtained in the presence of charcoal, e.g. 89% vs 59% for 1-nitro-2-(trifluoromethyl)benzene. The nature of the beneficial effect of charcoal is unclear.

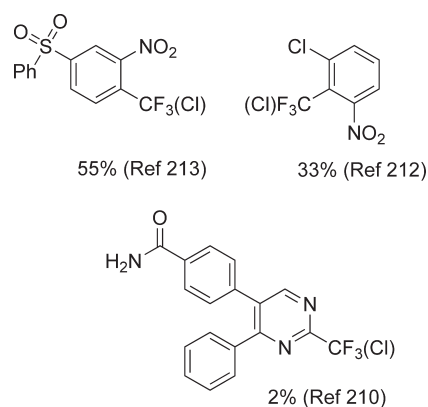
Scheme 13



More examples of trifluoromethylation with $\text{Cu}/\text{CF}_2\text{Br}_2$ have been reported^{209–214} to synthesize the compounds shown in Scheme 14.

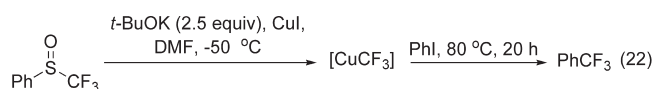
Fluoroform CHF_3 could be an ideal CF_3 source (see section 2), yet its use in aromatic trifluoromethylation has been limited. Direct cupration and zincation of CHF_3 even with strong Cu and Zn bases have been unsuccessful.⁸⁵ Deprotonation of CHF_3 with dimsyl potassium or *t*-BuOK usually leads to difluorocarbene,

Scheme 14



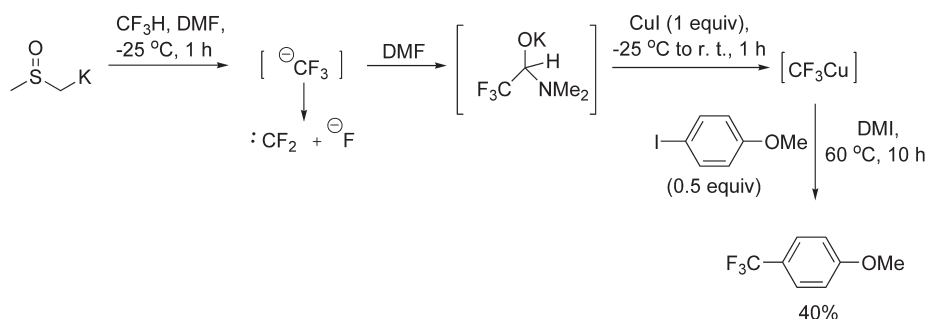
unless carried out at low temperatures in DMF, where the primary product, CF_3^- , is stabilized as its adduct (eq 2). The latter has been shown⁸⁵ to react with CuI to first produce $\text{Me}_2\text{NC(H)(CF}_3\text{)OCu}$ and then eventually CuCF_3 species (^{19}F NMR). These species are stable in 1:1 DMF/DMI at room temperature and have been shown to react with 4-iodoanisole to give 4-(trifluoromethyl)anisole in 40% yield (Scheme 15).

Phenyl trifluoromethyl sulfone and sulfoxide that may be prepared from CHF_3 have been used⁸⁶ to generate a “ CF_3^- ” synthon on treatment with *t*-BuOM ($\text{M} = \text{K, Na}$). In the presence of CuI at -50°C , a CuCF_3 species was formed that was then treated with PhI to give benzotrifluoride in 26% yield (eq 22).

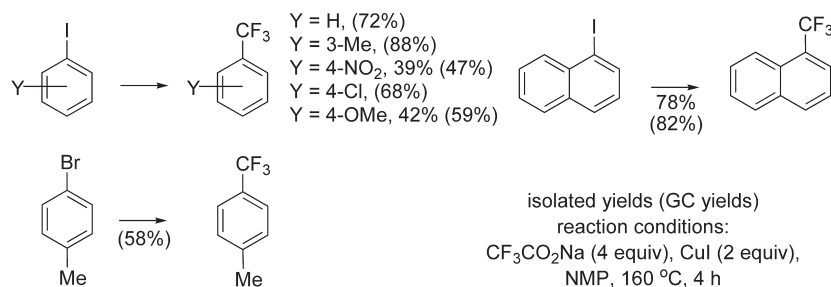


4.1.2. Trifluoroacetic and Fluorosulfonyldifluoroacetic Acid Derivatives as CF_3 Sources. In 1981, Kondo's group⁸¹ reported Cu-promoted decarboxylative trifluoromethylation of aryl halides with sodium trifluoroacetate, an inexpensive CF_3 source (Scheme 16). Although the reaction occurs under harsh conditions

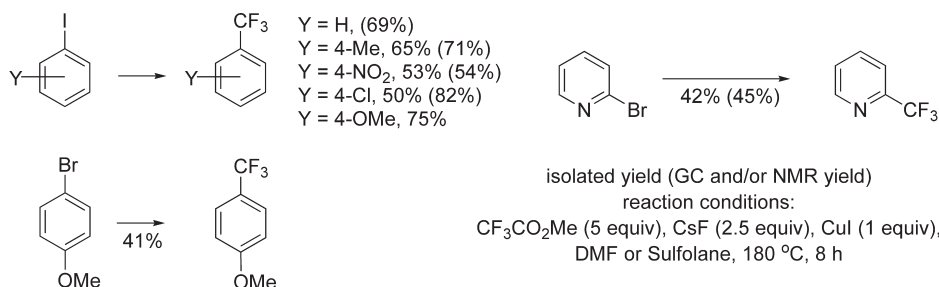
Scheme 15



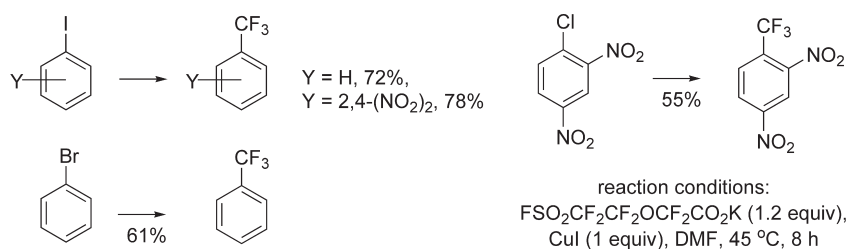
Scheme 16



Scheme 17



Scheme 18



and requires excess of CF₃COONa, good yields can be obtained. More publications quickly followed^{215,216} to report this type of trifluoromethylation for a broader range of aromatic and heteroaromatic halides, as well as mechanistic studies of the reaction. It has been shown that premade trifluoromethyl benzoate does not undergo decarboxylation under the coupling reaction conditions and that CF₃COONa produces fluoroform when heated in aqueous NMP, with CuI increasing the rate of decarboxylation.²¹⁶ The Hammett plot constructed using a series of substituted iodobenzenes in the reaction gave $\rho = 0.46$, pointing to an accelerating effect of electron-withdrawing groups. Numerous examples of aromatic trifluoromethylations with CF₃CO₂Na,^{217–221} CF₃CO₂K,²²² and CF₃CO₂NR₄^{222a,223} (R = Me, *n*-Bu) have been communicated.

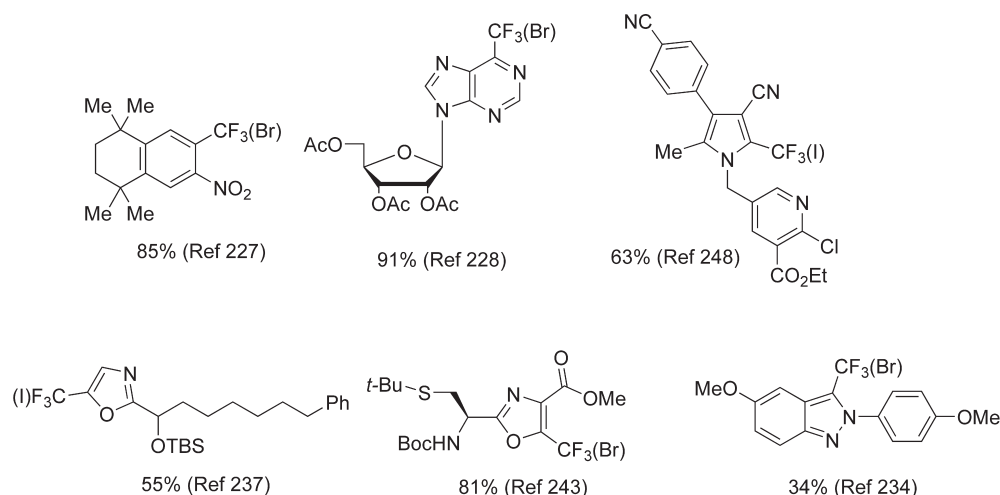
A drawback of the decarboxylative trifluoromethylation with alkali metal trifluoroacetates on a larger scale is their hygroscopicity and limited solubility in solvents suitable for the reaction. Also, in order to reach high conversions and yields, sodium trifluoroacetate must be used in large excess, up to 10-fold. To eliminate these problems, Langlois et al.⁸² recently developed a similar process employing methyl trifluoroacetate (Scheme 17). However, the Langlois method still employs high temperatures and uses a 5-fold excess of the trifluoromethylating agent and 2.5 equiv of CsF that is needed for the Krapcho-type decarboxylation step.

It has been found²²⁴ that FSO₂CF₂CF₂OCF₂CO₂K can easily decompose in the presence of CuI to generate reactive CF₃Cu at as low as 45 °C (Scheme 18). Although the sulfur-free analogues CF₃(OCF₂)_{*n*}CO₂M (*n* = 1, M = K, Na; *n* = 2, M = K) trifluoromethylate iodoarenes at a higher temperature (115 °C), the yields (¹⁹F NMR) are high, especially when CF₃OCF₂CO₂K is employed.²²⁵ Thus, iodobenzene, 1-iodonaphtalene, and 4-nitroiodobenzene gave the corresponding trifluoromethylated derivatives in 100%, 97%, and 86%, respectively. Less reactive 4-nitrobromobenzene was converted to 4-(trifluoromethyl)-1-nitrobenzene in only 25% yield under similar conditions.

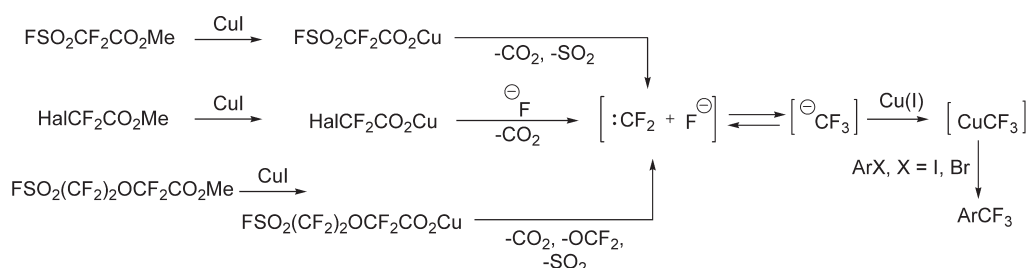
Chen and Wu¹⁰⁰ have found that FSO₂CF₂CO₂Me readily eliminates CO₂ and SO₂ in the presence of CuI in DMF at as low as 60–80 °C to produce CuCF₃ species that can be used for aromatic trifluoromethylation. This remarkable reaction can be *catalytic* in Cu and will be discussed in more detail in section 5 below. Surprisingly, numerous articles^{226–243} and patents^{210,221,244–263} report aromatic trifluoromethylation with FSO₂CF₂CO₂Me using *stoichiometric* rather than catalytic amounts of Cu, e.g., for the synthesis of compounds shown in Scheme 19. Chen's group has also reported^{264,265} Cu-promoted trifluoromethylation of bromoporphyrins with FSO₂CF₂CO₂Me in the presence of Pd₂(dba)₃·CHCl₃ (5–10 mol %) and, optionally,²⁶⁴ AsPh₃ (40 mol %). The presence of catalytic quantities of Pd has been reported^{264,265} as crucial for these trifluoromethylations to be successful. This interesting observation and the role of Pd are discussed in section 5 below.

Decarboxylative trifluoromethylation has also been performed with BrCF₂CO₂K²⁶⁶ or XCF₂CO₂Me, where X = Cl,^{96–98} Br,⁹⁸ I,^{98a} or FSO₂(CF₂)₂O.²⁶⁷ While the latter, FSO₂(CF₂)₂OCF₂CO₂Me, already contains a “masked” CF₃ fragment, the other halodifluoroacetates do not. Therefore, the trifluoromethylation with FSO₂(CF₂)₂OCF₂CO₂Me smoothly proceeds in the absence of an additional source of fluoride, whereas 1 equiv of KF is needed to achieve better yields when chloro-, bromo-, and iododifluoroacetic acid derivatives are used. Both FSO₂(CF₂)₂OCF₂CO₂Me and ClCF₂CO₂Me undergo decarboxylation at higher temperatures (up to 120 °C) than BrCF₂CO₂Me and ICF₂CO₂Me, which decompose at 85–90 °C. All four reagents give comparable yields of ca. 80% for PhI and simple substituted iodobenzenes. It has been proposed that the mechanism of these reactions (Scheme 20) involves the formation of the corresponding Cu(I) carboxylate, followed by decarboxylation and generation of difluorocarbene, which, in the presence of fluoride, gives rise to a CF₃Cu species. However, attempts to trap the proposed carbene intermediate with olefins have been unsuccessful. Methyl chlorodifluoroacetate has been

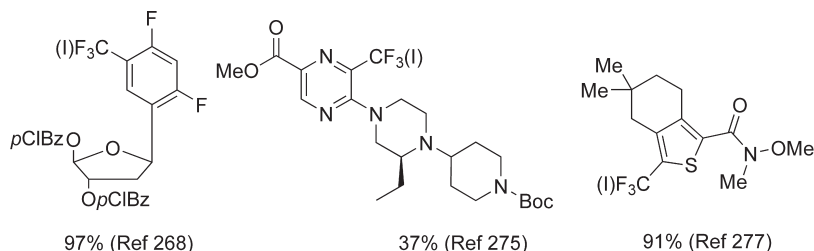
Scheme 19



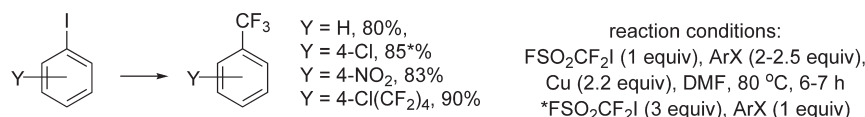
Scheme 20



Scheme 21



Scheme 22



widely used^{268–282} in the synthesis of important intermediates and compounds, some of which are shown in Scheme 21.

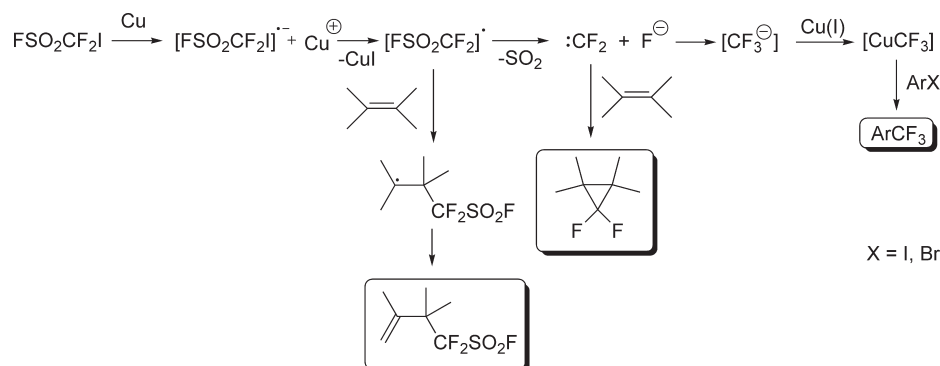
Closely related to the reactions employing FSO₂CF₂CO₂Me and FSO₂(CF₂)₂OCF₂CO₂Me are the trifluoromethylations performed with fluorosulfonyl difluoromethyl iodide FSO₂CF₂I and Cu metal (Scheme 22).²⁸³

A single electron transfer scavenger (4-nitrobenzene) and a free radical inhibitor (hydroquinone) have been found to partially suppress the reaction. Difluorocarbene is believed to

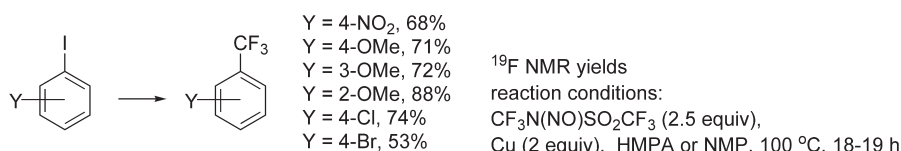
mediate these transformations that produce detectable quantities of 1,1-difluoro-2,2,3,3-tetramethylcyclopropane when carried out in the presence of 2,3-dimethylbut-2-ene. A product of addition of the FSO₂CF₂ radical to an olefin has also been detected. A proposed mechanism accounting for these observations is shown in Scheme 23.

Another CF₃ source for aromatic trifluoromethylation, CF₃N(NO)SO₂CF₃, has been developed by Umemoto.²⁸⁴ This reagent is prepared in two steps from CF₃NO, NH₂OH, and

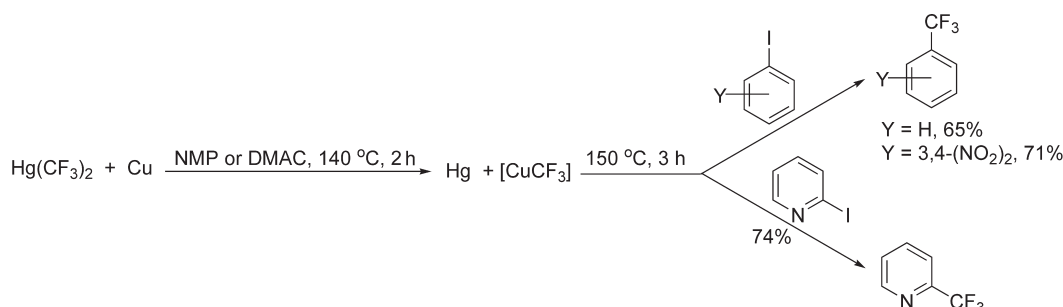
Scheme 23



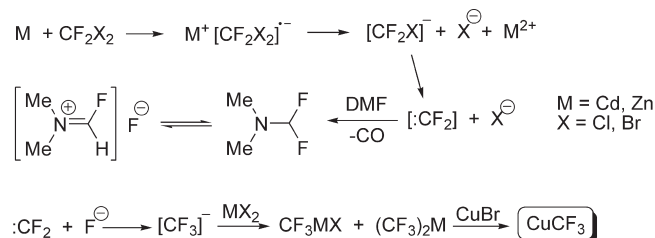
Scheme 24



Scheme 25



Scheme 26



CF₃SO₂F in overall 58% yield. The thermal decomposition of CF₃N(NO)SO₂CF₃ in the presence of Cu metal and an aromatic halide in HMPA or NMP affords the corresponding benzotrifluoride (Scheme 24). It has been briefly mentioned without experimental details that CF₃SO₂Cl reacts with Cu in DMAC to generate CF₃Cu that can trifluoromethylate 1-chloro-2,4-dinitrobenzene.²⁸⁵

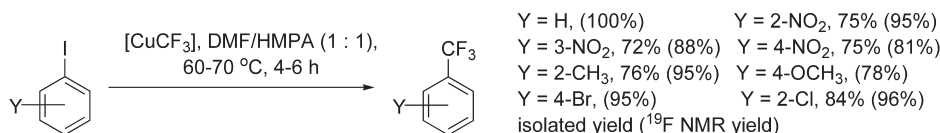
4.1.3. Trifluoromethylcopper Reagents via Transmetalation. As described in section 3.3 above, the first example of

CF₃ transfer to Cu from another metal was reported by Yagupolskii's group in 1980.¹⁶⁶ They found that Hg(CF₃)₂ reacted with Cu powder to give a reactive CuCF₃ species that trifluoromethylated iodoaromatic compounds (Scheme 25).

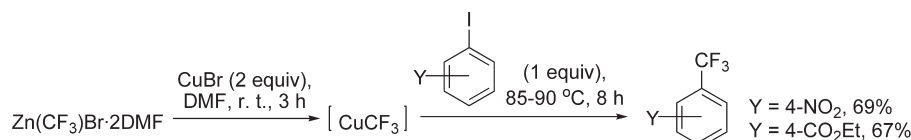
Trifluoromethyl derivatives of Cd(II) and Zn(II) have been used to generate CuCF₃ via transmetalation with Cu(I) halides. Burton and Wiemers^{95,167} have reported that Cd(II) and Zn(II) trifluoromethyl reagents can be prepared from difluorodihalomethanes (CF₂Br₂, CF₂Cl₂, CF₂BrCl) and the corresponding metal in DMF. It has been proposed that the mechanism of these reactions (Scheme 26) involves reduction of CF₂X₂ to give difluorocarbene. The latter is captured by DMF to give CO and α,α-difluorotrimethylamine that is known to be a fluoride source. Addition of the F[−] to :CF₂ leads to "CF₃[−]" which forms M(CF₃)_nX_{2−n} (M = Cd, Zn; X = Cl, Br; n = 1, 2). These reagents readily transfer the CF₃ group to copper of CuBr in DMF, the reaction being much faster for cadmium than for zinc. The formation of CuCF₃ from the CdCF₃ species readily occurs even at −50 °C.

The Wiemers–Burton ¹⁹F NMR studies of the CF₃Cu species generated on the transmetalation are discussed in

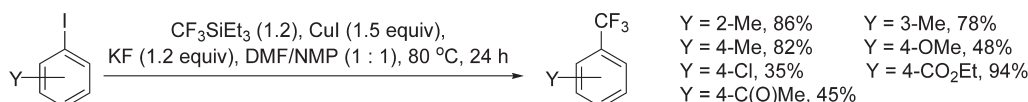
Scheme 27



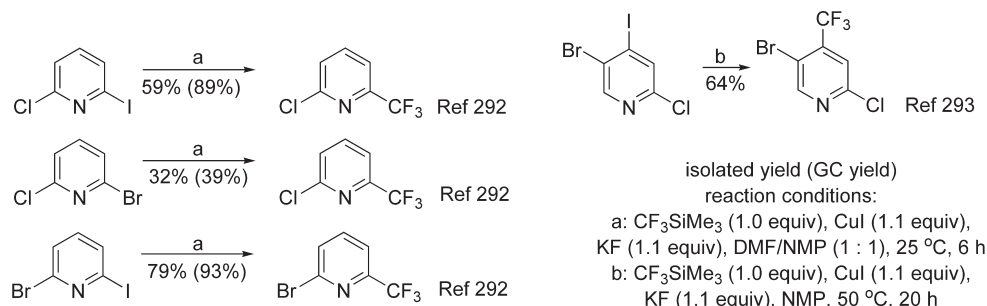
Scheme 28



Scheme 29



Scheme 30



section 3.3 above. Although the system is very complex,^{167,286} in DMF–HMPA the Cu reagent is stable and smoothly trifluoromethylates aryl iodides in high yields (Scheme 27).

Both ZnCF₃^{114,287,288} and CdCF₃^{289,290} reagents have been used by other groups for Cu-promoted aromatic trifluoromethylation. Very recently, Kremlev et al.¹¹⁴ reported the generation of CuCF₃ solutions from Zn(CF₃)Br·2DMF and CuBr in DMF. The Zn reagent solution that was prepared from CF₃Br and zinc dust can be stored for a long period (6–12 months) under an inert atmosphere at low temperatures and used when desired for aromatic trifluoromethylation, e.g., Scheme 28. When less reactive aryl halides were used, the coupling was less selective because of the competing transformation of CuCF₃ to CuCF₂CF₃. As a result, the formation of both trifluoromethylated and pentafluoroethylated products was observed.

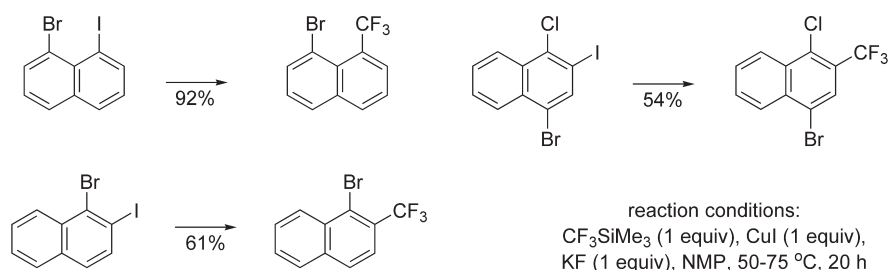
4.1.4. Ruppert's Reagent CF₃SiMe₃ and its Ethyl Analogue CF₃SiEt₃. Soon after CF₃SiMe₃ was reported to be an excellent reagent for trifluoromethylation of carbonyl compounds, its ethyl analogue CF₃SiEt₃ was found to be useful to generate CuCF₃ species for coupling with iodoarenes (Scheme 29).²⁹¹

This methodology has been applied, with minor modifications, for the synthesis of trifluoromethyl-substituted pyridines from polyhalopyridines.^{292–295} Under similar conditions, bromopyridines react ca. 50 times slower, while chloropyridines remain intact. Unsurprisingly, when different halogens are present on the ring, it is the heavier halide that is selectively displaced (Scheme 30). The same trend has been observed for polyhalonaphthalenes (Scheme 31).²⁹⁶

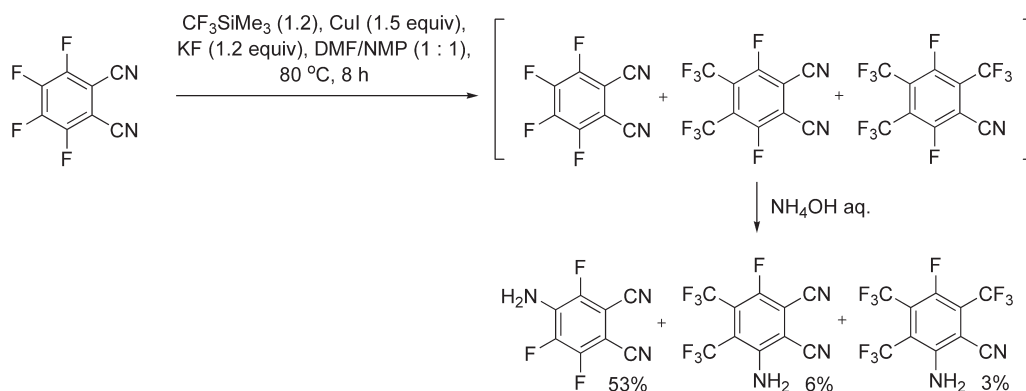
In highly activated aromatic systems bearing several strong electron-withdrawing substituents, C–F and even C–CN bonds can be trifluoromethylated, albeit in low yield (Scheme 32).^{297a} It is worth noting, however, that most closely related, highly electrophilic substrates such as pentafluoropyridine, perfluorotoluene, and perfluorobiphenyl undergo facile nucleophilic displacement of fluorine with CF₃ upon treatment with [Me₃SiF₂][–]-activated CF₃SiMe₃ in the absence of copper or any other metal catalyst/promoter at room temperature.^{297b}

Kolomeitsev and co-workers¹⁶⁸ have recently prepared a series of very interesting polytrifluoromethylated benzenes using CuCF₃ pregenerated from CF₃SiMe₃, CuBr, and KF in DMF at 0 °C and additionally stabilized with DMI. Treatment of C₆I₆

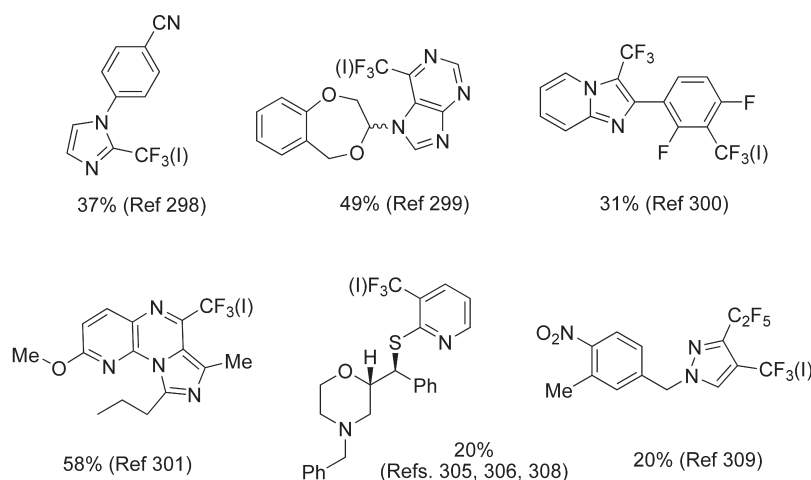
Scheme 31



Scheme 32



Scheme 33



with this reagent solution afforded $\text{C}_6(\text{CF}_3)_6$ (45%) along with $\text{C}_6(\text{CF}_3)_5(\text{OK})$ (20%) and $\text{C}_6\text{H}(\text{CF}_3)_5$ (14%). In recent years Ruppert's reagent has become a particularly popular CF_3 source for Cu-promoted trifluoromethylation of aryl halides.^{298–325} Some examples of important compounds made by this method are shown in Scheme 33.

4.1.5. Well-Defined CF_3Cu Complexes. The first example of aromatic trifluoromethylation with a well-defined CuCF_3 complex was reported by Willert-Porada, Burton, and Baenziger¹²⁷ in 1989. When structurally characterized $[(\text{Et}_2\text{NCS}_2)\text{Cu}(\text{CF}_3)_2]$ (see

section 3.3) was heated with iodobenzene, 4-bromoanisole, or 1-bromo-4-iodobenzene, the corresponding trifluoromethylated arenes were formed. As the trifluoromethylating agent was a $\text{Cu}(\text{III})$ compound, it is likely that it underwent reduction prior to reaction with the aromatic electrophiles.

Vicic and co-workers^{60,170} have recently prepared and characterized a series of new CF_3Cu complexes stabilized by NHC ligands (see section 3.3). The $\text{Me}_3\text{Si-IPrCuCF}_3$ complex has been found to slowly react with PhI at room temperature to give PhCF_3 in 33% yield after 44 h (eq 23).⁶⁰

Table 2. Copper-Promoted Trifluoromethylation Reactions of Aryl Iodides



Aryl Iodide	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	CF ₃ I (1 equiv), Cu (3.8 equiv)	ArI (1.4 equiv), DMF, 150 °C, 12 h		45 (isol.)	56
	CF ₃ I (4.1 equiv), Cu (5.3 equiv)	DMF, 130–140 °C, 20 h		72 (isol.)	189
	CF ₃ Br (6 equiv), Cu (4 equiv)	HMPA, 130 °C, 20 h		11 (isol.)	204
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		87 (GC)	216
	CF ₃ CO ₂ Me (5 equiv), CsF (2.5 equiv), CuI (1 equiv)	DMF, 180 °C, 8 h		69 (GC and NMR)	82
	CICF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 100–120 °C, 8 h		88 (isol.)	97
	BrCF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 85–90 °C, 5 h		81 (isol.)	98a
	ICF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 80 °C, 5 h		75 (GC)	98a
	FSO ₂ CF ₂ I (1 equiv), Cu (2.2 equiv)	ArI (2 equiv), DMF, 80 °C, 7 h		80 (isol.)	283
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ K (1.2 equiv), CuI (1 equiv)	DMF, 45 °C, 8 h		72 (isol.)	224
	CF ₃ OCF ₂ CO ₂ K (1.4 equiv), CuI (1.4 equiv)	DMF, 115 °C, 3 h		100 (¹⁹ F NMR)	225
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 100 °C, 8 h		80 (isol.)	267
	Hg(CF ₃) ₂ (2 equiv), Cu (8 equiv)	1. NMP, 140 °C, 2 h 2. Addition of ArI, 150 °C, 3 h		65 (isol.)	166
	Cd (5.7 equiv), CF ₂ BrCl (3 equiv)	1. DMF, r. t., 2 h, filtration 2. HMPA, CuBr (1.4 equiv), 0 °C, then ArI, 60–70 °C, 4–6 h		100 (¹⁹ F NMR)	167
	Si/PrCu(O <i>t</i> -Bu), CF ₃ SiMe ₃ (2 equiv)	ArI (5 equiv), DMF, r. t., 112 h		94 (¹⁹ F NMR)	60
	[(SiMe ₃) ₂ Cu][(CF ₃) ₂ Cu]	ArI (10 equiv), Benzene/DMI (5 : 1), 50 °C, 28 h		86 (¹⁹ F NMR)	170
	CF ₃ I (11.9 equiv), Cu (7.8 equiv)	DMF, 140 °C, 24 h		32 (isol.)	189
	CF ₃ CO ₂ Na (8 equiv), CuI (4 equiv)	NMP, 160 °C, 4 h		93 (GC)	216
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 100 °C, 8 h		62 (isol.)	267
	CF ₃ I (3.3 equiv), Cu (3.4 equiv)	DMF, 130–140 °C, 11 h		28 (isol.)	189
	Cd (5.7 equiv), CF ₂ BrCl (3 equiv)	1. DMF, r. t., 2 h, filtration 2. HMPA, CuBr (1.4 equiv), 0 °C, then ArI, 60–70 °C, 4–6 h		76 (isol.), 95 (¹⁹ F NMR)	167
	CF ₃ SiEt ₃ (1.2 equiv), CuI (1.5 equiv), KF (1.2 equiv)	DMF/NMP (1 : 1), 80 °C, 24 h		86 (NMR, GC or isol.)	291
	CF ₃ I (3.3 equiv), Cu (3.4 equiv)	DMF, 130–140 °C, 20 h		68 (isol.)	189
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		88 (GC)	81
	CF ₃ SiEt ₃ (1.2 equiv), CuI (1.5 equiv), KF (1.2 equiv)	DMF/NMP (1 : 1), 80 °C, 24 h		78 (NMR, GC or isol.)	291
	CF ₃ CO ₂ Me (5 equiv), CsF (2.5 equiv), CuI (1 equiv)	DMF, 180 °C, 8 h		65 (isol.), 71 (GC and NMR)	82
	CF ₃ SiEt ₃ (1.2 equiv), CuI (1.5 equiv), KF (1.2 equiv)	DMF/NMP (1 : 1), 80 °C, 24 h		82 (NMR, GC or isol.)	291
	CF ₃ CO ₂ Na (2.5 equiv), CuI (1.5 equiv)	HMPA, 150–180 °C, 15 h		41 (isol.)	215

Table 2. Continued

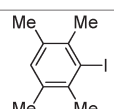
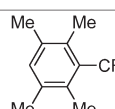
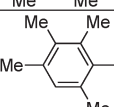
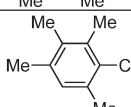
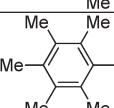
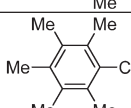
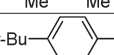
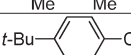
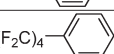
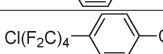
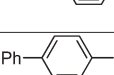
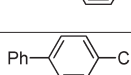
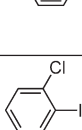
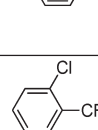
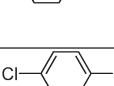
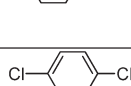
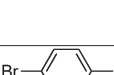
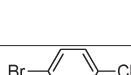
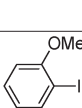
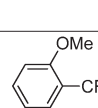
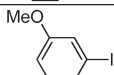
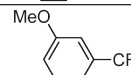
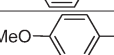
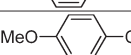
Aryl Iodide	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	CF ₃ CO ₂ Na (2.5 equiv), CuI (1.5 equiv)	HMPA, 150–180 °C, 15 h		32 (isol.)	215
	CF ₃ CO ₂ Na (2.5 equiv), CuI (1.5 equiv)	HMPA, 150–180 °C, 15 h		38 (isol.)	215
	CF ₃ CO ₂ Na (2.5 equiv), CuI (1.5 equiv)	HMPA, 150–180 °C, 15 h		38 (isol.)	215
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		60 (GC)	216
	[(SiMes) ₂ Cu][(CF ₃) ₂ Cu]	ArI (10 equiv), Benzene/DMI (5 : 1), 50 °C, 28 h		70 (¹⁹ F NMR)	170
	FSO ₂ CF ₂ I (1 equiv), Cu (2.2 equiv)	ArI (1.8 equiv), DMF, 80 °C, 7 h		90 (isol.)	283
	Si/PrCu(O <i>t</i> -Bu), CF ₃ SiMe ₃ (2 equiv)	ArI (5 equiv), DMF, r. t., 112 h		99 (¹⁹ F NMR)	60
	[(SiMes) ₂ Cu][(CF ₃) ₂ Cu]	ArI (10 equiv), Benzene/DMI (5 : 1), 50 °C, 28 h		93 (¹⁹ F NMR)	170
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		87 (GC)	216
	Cd (5.7 equiv), CF ₂ BrCl (3 equiv)	1. DMF, r. t., 2 h, filtration 2. HMPA, CuBr (1.4 equiv), 0 °C, then ArI, 60–70 °C, 4–6 h		84 (isol.), 96 (¹⁹ F NMR)	167
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		68 (GC)	81
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		98 (GC)	216
	CF ₃ CO ₂ Me (5 equiv), CsF (2.5 equiv), CuI (1 equiv)	DMF, 180 °C, 8 h		50 (isol.), 82 (GC and NMR)	82
	FSO ₂ CF ₂ I (3 equiv), Cu (6 equiv)	DMF, 80 °C, 6 h		85 (isol.)	283
	ClCF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 100 °C, 8 h		81 (isol.)	97
	CF ₃ N(NO)SO ₂ CF ₃ (2.5 equiv), Cu (5 equiv)	NMP/CH ₃ CN (5 : 2), 100 °C, 19 h		74 (¹⁹ F NMR)	284
	CF ₃ SiEt ₃ (1.2 equiv), CuI (1.5 equiv), KF (1.2 equiv)	DMF/NMP (1 : 1), 80 °C, 24 h		35 (NMR, GC or isol.)	291
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 120 °C, 8 h		82 (isol.)	267
	CF ₃ N(NO)SO ₂ CF ₃ (2.5 equiv), Cu (5 equiv)	NMP/CH ₃ CN (5 : 2), 100 °C, 19 h		53 (¹⁹ F NMR)	284
	Cd (5.7 equiv), CF ₂ BrCl (3 equiv)	1. DMF, r. t., 2 h, filtration 2. HMPA, CuBr (1.4 equiv), 0 °C, then ArI, 60–70 °C, 4–6 h		95 (¹⁹ F NMR)	167
	CF ₃ N(NO)SO ₂ CF ₃ (2.5 equiv), Cu (5 equiv)	NMP/CH ₃ CN (5 : 2), 100 °C, 19 h		88 (¹⁹ F NMR)	284
	CF ₃ N(NO)SO ₂ CF ₃ (2.5 equiv), Cu (5 equiv)	NMP/CH ₃ CN (5 : 2), 100 °C, 19 h		72 (¹⁹ F NMR)	284
	CF ₃ I (12 equiv), Cu (11 equiv)	DMF, 130–140 °C, 20 h		86 (isol.)	189
	Copper anode, CF ₃ Br (excess)	1. PBu ₃ (2 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, –15 °C, 6 h 2. ArI, DMF, 90 °C, 3 h		92 (GC)	206
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		90 (GC)	206

Table 2. Continued

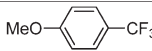
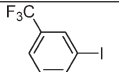
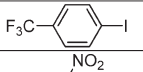

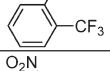

Aryl Iodide	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	CF ₃ H (2 equiv)	1. Potassium dimsylate (4 equiv), CF ₃ H (2 equiv), DMF, −25 °C, 1 h 2. CuI (2 equiv), −25 °C to r. t. 3. DMI, 60 °C, 10 h		40 (¹⁹ F NMR)	85
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		42 (isol.), 59 (GC)	81
	CF ₃ CO ₂ Me (5 equiv), CsF (2.5 equiv), CuI (1 equiv)	Sulfolane, 180 °C, 8 h		79 (isol.)	82
	CF ₃ N(NO)SO ₂ CF ₃ (2.5 equiv), Cu (5 equiv)	HMPA/CH ₃ CN (5 : 2), 100 °C, 18 h		71 (¹⁹ F NMR)	284
	Cd (5.7 equiv), CF ₂ BrCl (3 equiv)	1. DMF, r. t., 2 h, filtration 2. HMPA, CuBr (1.4 equiv), 0 °C, then ArI, 60–70 °C, 4–6 h		78 (¹⁹ F NMR)	167
	CF ₃ SiEt ₃ (1.2 equiv), CuI (1.5 equiv), KF (1.2 equiv)	DMF/NMP (1 : 1), 80 °C, 24 h		48 (NMR, GC or isol.)	291
	SiPrCu(O <i>i</i> -Bu), CF ₃ SiMe ₃ (2 equiv)	ArI (5 equiv), DMF, r. t., 112 h		91 (¹⁹ F NMR)	60
	[(SiMe ₃) ₂ Cu][(CF ₃) ₂ Cu]	ArI (10 equiv), Benzene/DMI (5 : 1), 50 °C, 28 h		89 (¹⁹ F NMR)	170
	CF ₃ I (4 equiv), Cu (3.6 equiv)	DMF, 140 °C, 24 h		80 (isol.)	189
	CF ₃ I (7.1 equiv), Cu (4.6 equiv)	DMF, 125–135 °C, 12 h		62 (isol.)	189
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		73 (GC)	216
	Cd (5.7 equiv), CF ₂ BrCl (3 equiv)	1. DMF, r. t., 2 h, filtration 2. HMPA, CuBr (1.4 equiv), 0 °C, then ArI, 60–70 °C, 4–6 h		75 (isol.), 95 (¹⁹ F NMR)	167
	Cd (5.7 equiv), CF ₂ BrCl (3 equiv)	1. DMF, r. t., 2 h, filtration 2. HMPA, CuBr (1.4 equiv), 0 °C, then ArI, 60–70 °C, 4–6 h		72 (isol.), 88 (¹⁹ F NMR)	167
	CF ₃ I (7.1 equiv), Cu (10.8 equiv)	DMF, 135 °C, 30 h		51 (isol.)	189
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		39 (isol.), 47 (GC)	81
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		64 (GC)	216
	CF ₃ CO ₂ Me (5 equiv), CsF (2.5 equiv), CuI (1 equiv)	Sulfolane, 180 °C, 8 h		53 (isol.), 54 (GC and NMR)	82
	ClCF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 100 °C, 8 h		89 (isol.)	97
	BrCF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 85–90 °C, 5 h		80 (isol.)	98a
	FSO ₂ CF ₂ I (1 equiv), Cu (2.2 equiv)	ArI (2.5 equiv), DMF, 80 °C, 6 h		83 (isol.)	283
	CF ₃ OCF ₂ CO ₂ K (1.1 equiv), CuI (1.2 equiv)	DMF, 115 °C, 3 h		86 (¹⁹ F NMR)	225
	CF ₃ N(NO)SO ₂ CF ₃ (2.5 equiv), Cu (5 equiv)	HMPA/CH ₃ CN (5 : 2), 100 °C, 18 h		68 (¹⁹ F NMR)	284
	Hg(CF ₃) ₂ (2 equiv), Cu (8 equiv)	1. NMP, 140 °C, 2 h, filtration 2. Addition of ArI, 150 °C, 3 h		88 (isol.)	166
	Cd (5.7 equiv), CF ₂ BrCl (3 equiv)	1. DMF, r. t., 2 h, filtration 2. HMPA, CuBr (1.4 equiv), 0 °C, then ArI, 60–70 °C, 4–6 h		75 (isol.), 81 (¹⁹ F NMR)	167
	Zn(CF ₃)Br·2DMF (1 equiv), CuBr (2 equiv)	1. DMF, r. t., 3 h 2. Addition of ArI, 85–90 °C, 8 h		69 (isol.)	114
	CF ₃ SiEt ₃ (1.2 equiv), CuI (1.5 equiv), KF (1.2 equiv)	DMF/NMP (1 : 1), 80 °C, 24 h		99 (GC)	291

Table 2. Continued

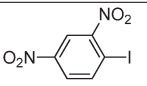
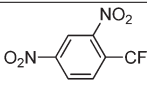
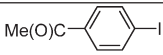
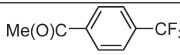
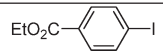
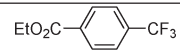




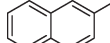
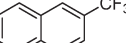
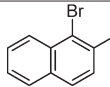
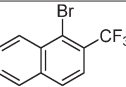
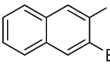
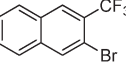
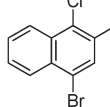
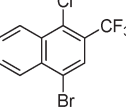





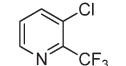

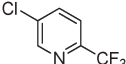

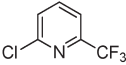
Aryl Iodide	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	Hg(CF ₃) ₂ (2 equiv), Cu (8 equiv)	1. NMP, 140 °C, 2 h, filtration 2. Addition of ArI, 150 °C, 3 h		71 (isol.)	166
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ K (1.2 equiv), CuI (1 equiv)	DMF, 45 °C, 6 h		78 (isol.)	224
	CF ₃ SiEt ₃ (1.2 equiv), CuI (1.5 equiv), KF (1.2 equiv)	DMF/NMP (1 : 1), 80 °C, 24 h		45 (NMR, GC or isol.)	291
	Zn(CF ₃)Br·2DMF (1 equiv), CuBr (2 equiv)	1. DMF, r. t., 3 h 2. Addition of ArI, 85–90 °C, 8 h		67 (isol.)	114
	CF ₃ SiEt ₃ (1.2 equiv), CuI (1.5 equiv), KF (1.2 equiv)	DMF/NMP (1 : 1), 80 °C, 24 h		94 (NMR, GC or isol.)	291
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		98 (GC)	206
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		78 (isol.), 82 (GC)	81
	ClCF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 110–120 °C, 8 h		94 (isol.)	97
	BrCF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 85–90 °C, 5 h		84 (isol.)	98a
	FSO ₂ CF ₂ I (1 equiv), Cu (2.2 equiv)	ArI (2 equiv), DMF, 80 °C, 6.5 h		84 (isol.)	283
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ K (1.2 equiv), CuI (1 equiv)	DMF, 45 °C, 8 h		61 (isol.)	224
	CF ₃ OCF ₂ CO ₂ K (1 equiv), CuI (1.1 equiv)	DMF, 115 °C, 3 h		97 (¹⁹ F NMR)	225
	CF ₃ SiMe ₃ (1 equiv), CuI (1 equiv), KF (1 equiv)	NMP, 75 °C, 20 h		92 (isol.)	296
	CF ₃ SiEt ₃ (1.2 equiv), CuI (1.5 equiv), KF (1.2 equiv)	DMF/NMP (1 : 1), 80 °C, 24 h		94 (NMR, GC or isol.)	291
	CF ₃ SiMe ₃ (1 equiv), CuI (1 equiv), KF (1 equiv)	NMP, 50 °C, 20 h		61 (isol.)	296
	CF ₃ SiMe ₃ (1 equiv), CuI (1 equiv), KF (1 equiv)	NMP, 50 °C, 20 h		48 (isol.)	296
	CF ₃ SiMe ₃ (1 equiv), CuI (1 equiv), KF (1 equiv)	NMP, 50 °C, 20 h		54 (isol.)	296
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		46 (GC)	216
	Zn(CF ₃)Br·2DMF (1 equiv), CuBr (1 equiv)	1. DMF, r. t., 3 h 2. Addition of ArI, 60 °C, 5 h		80 (¹⁹ F NMR)	114
	Hg(CF ₃) ₂ (2 equiv), Cu (8 equiv)	1. DMAC, 140 °C, 2 h 2. Addition of ArI, 150 °C, 3 h		74 (isol.)	166
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		68 (isol.), 92 (GC)	292
	Zn(CF ₃)Br·2DMF (1 equiv), CuBr (2 equiv)	1. DMF, r. t., 3 h 2. Addition of ArI, 80 °C, 6 h		93 (¹⁹ F NMR)	114
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	NMP, 50 °C, 6 h		46% (isol.)	295
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	NMP, 50 °C, 20 h		72 (isol.)	293
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		59 (isol.), 89 (GC)	292

Table 2. Continued

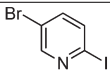
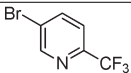
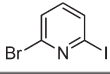
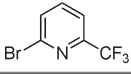
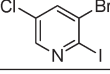
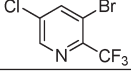
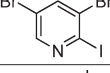
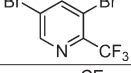




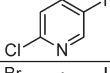
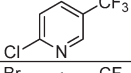
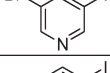
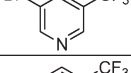
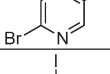
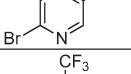






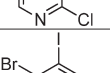
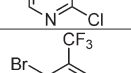
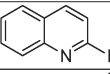
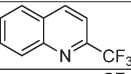
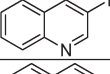
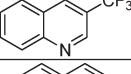
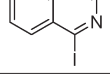
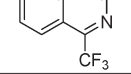
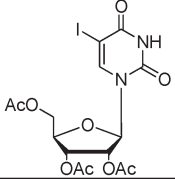
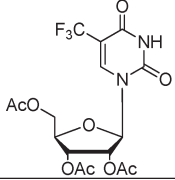
Aryl Iodide	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		69 (isol.), 85 (GC)	292
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		79 (isol.), 93 (GC)	292
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	NMP, 50 °C, 20 h		69 (isol.)	293
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		59 (isol.), 87 (GC)	292
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		23 (isol.), 45 (GC)	292
	Si/PrCu(Or-Bu), CF ₃ SiMe ₃ (2 equiv)	Arl (5 equiv), DMF, r. t., 112 h		94 (¹⁹ F NMR)	60
	[(SiMes) ₂ Cu][(CF ₃) ₂ Cu]	Arl (10 equiv), Benzene/DMI (5 : 1), 50 °C, 28 h		88 (¹⁹ F NMR)	170
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		67 (isol.), 91 (GC)	292
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		85 (GC)	216
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		48 (isol.), 72 (GC)	292
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		29 (isol.), 42 (GC)	292
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		25 (isol.), 48 (GC)	292
	Si/PrCu(Or-Bu), CF ₃ SiMe ₃ (2 equiv)	Arl (5 equiv), DMF, r. t., 112 h		99 (¹⁹ F NMR)	60
	[(SiMes) ₂ Cu][(CF ₃) ₂ Cu]	Arl (10 equiv), Benzene/DMI (5 : 1), 50 °C, 28 h		57 (¹⁹ F NMR)	170
	CF ₃ SiMe ₃ (1 equiv), CuI (1 equiv), KF (1 equiv)	NMP, 50 °C, 20 h		69 (isol.)	294
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		68 (isol.), 90 (GC)	292
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	NMP, 50 °C, 20 h		64 (isol.)	293
	CF ₃ I (4.3 equiv), Cu (4 equiv)	DMF, 135 °C, 20 h		60 (isol.)	189
	CF ₃ I (6.5 equiv), Cu (2.6 equiv)	CH ₃ CN, 120 °C, 20 h		30 (isol.)	189
	CF ₃ I (9.2 equiv), Cu (12 equiv)	DMF, 130–140 °C, 20 h		8 (isol.)	189
	CF ₃ I (18 equiv), Cu (24 equiv)	HMPA, 110 °C, 40 h		38 (isol.)	191

Table 2. Continued

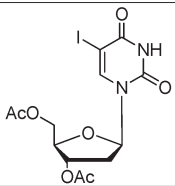
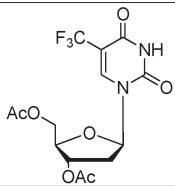
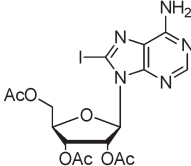
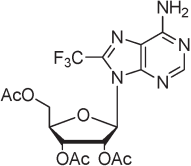
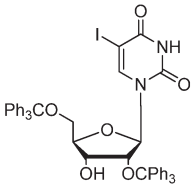
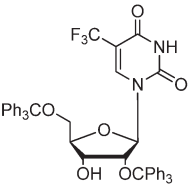
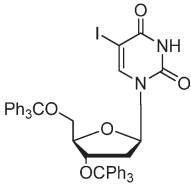
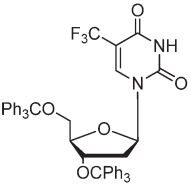
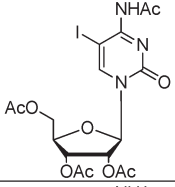
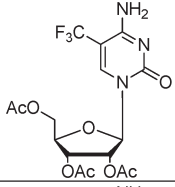
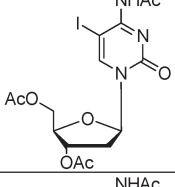
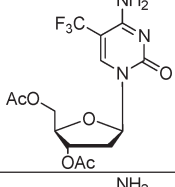
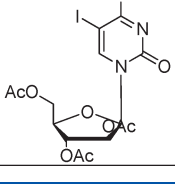
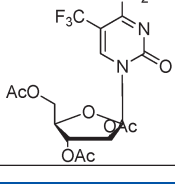
Aryl Iodide	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	CF ₃ I (16 equiv), Cu (21 equiv)	HMPA, 110 °C, 40 h		54 (isol.)	191
	CF ₃ I (49 equiv), Cu (69 equiv)	HMPA, r. t., 12 h		46 (isol.)	190
	CF ₃ I (21 equiv), Cu (34 equiv)	HMPA, 45 °C, 12 h		62 (isol.)	190
	CF ₃ I (29 equiv), Cu (46 equiv)	HMPA, 45 °C, 12 h		89 (isol.)	190
	CF ₃ I (18 equiv), Cu (28 equiv)	HMPA, 45 °C, 12 h		59 (isol.)	190
	CF ₃ I (29 equiv), Cu (46 equiv)	HMPA, 45 °C, 12 h		62 (isol.)	190
	CF ₃ I (26 equiv), Cu (41 equiv)	HMPA, 45 °C, 12 h		39 (isol.)	190

Table 3. Copper-Promoted Trifluoromethylation Reactions of Aryl Bromides



Aryl Bromide	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	CF ₃ I (3 equiv), Cu (6 equiv)	Pyridine, 130–140 °C, 20 h		11 (isol.)	189
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		68 (GC)	216
	ClCF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 110–120 °C, 8 h		60 (isol.)	97

Table 3. Continued



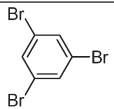
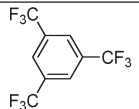
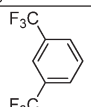
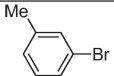
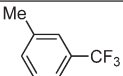


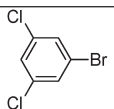
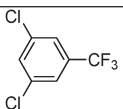
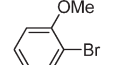
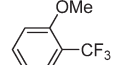
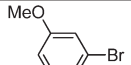
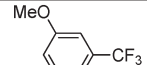
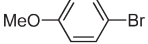
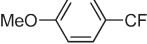
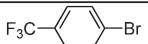
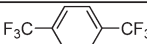
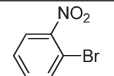
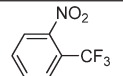
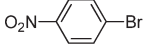
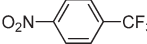


Aryl Bromide	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	BrCF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 85–90 °C, 5 h		67 (isol.)	98a
	ICF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 80 °C, 5 h		61 (GC)	98a
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ K (1.2 equiv), CuI (1 equiv)	DMF, 45 °C, 8 h		61 (isol.)	224
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 110 °C, 8 h		73 (isol.)	267
	CF ₃ CO ₂ Na (12 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		48 (GC)	216
				41 (GC)	
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		58 (GC)	81
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		78 (GC)	216
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		32 (GC)	206
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		70 (GC)	206
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		32 (GC)	206
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		23 (GC)	206
	Copper anode, CF ₃ Br (excess)	1. PBu ₃ (2 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, –15 °C, 6 h 2. ArI, DMF, 90 °C, 3 h		15 (GC)	206
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		32 (GC)	206
	CF ₃ CO ₂ Me (5 equiv), CsF (2.5 equiv), CuI (1 equiv)	DMF, 180 °C, 8 h		41	82
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		62 (GC)	216
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		30 (GC)	207b
	Copper anode, CF ₃ Br (excess)	1. PBu ₃ (2 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, –15 °C, 6 h 2. ArI, DMF, 90 °C, 3 h		70 (GC)	206
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		98 (GC)	206
	CF ₃ OCF ₂ CO ₂ K (1 equiv), CuI (1 equiv)	DMF, 115 °C, 3 h		25 (¹⁹ F NMR)	225
	Copper anode, CF ₃ Br (excess)	1. PBu ₃ (2 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, –15 °C, 6 h 2. ArI, DMF, 90 °C, 3 h		72 (GC)	206

Table 3. Continued

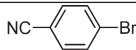
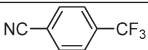

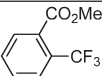
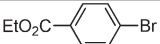
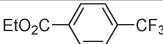


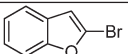
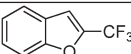









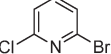
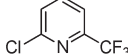
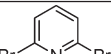
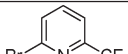


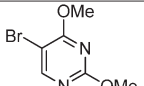
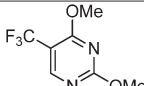
Aryl Bromide	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		91 (GC)	206
	Copper anode, CF ₃ Br (excess)	1. PBu ₃ (2 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, −15 °C, 6 h 2. ArI, DMF, 90 °C, 3 h		98 (GC)	206
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		54 (GC)	206
	Copper anode, CF ₃ Br (excess)	1. PBu ₃ (2 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, −15 °C, 6 h 2. ArI, DMF, 90 °C, 3 h		52 (GC)	206
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		56 (GC)	206
	FSO ₂ CF ₂ I (1 equiv), Cu (2.2 equiv)	ArBr (2.5 equiv), DMF, 80 °C, 7 h		78 (isol.)	283
	BrCF ₂ CO ₂ Me (2 equiv), KF (1 equiv), CuI (1 equiv)	DMF, 85–90 °C, 5 h		71 (isol.)	98a
	CF ₃ N(NO)SO ₂ CF ₃ (2.5 equiv), Cu (5 equiv)	HMPA/CH ₃ CN (5 : 2), 100 °C, 18 h		16 (¹⁹ F NMR)	284
	CF ₃ I (7 equiv), Cu (5 equiv)	DMF, 110–130 °C, 20 h		53 (isol.)	192
	CF ₃ I (7 equiv), Cu (5 equiv)	DMF, 110–130 °C, 20 h		60 (isol.)	192
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h	 +  1 : 1	88 (GC)	206
	Copper anode, CF ₃ Br (excess)	1. tmeda (2 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, −15 °C, 6 h 2. ArI, DMF, 90 °C, 3 h		98 (GC)	206
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		95 (GC)	206
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		41 (GC)	81
	CF ₃ CO ₂ Me (5 equiv), CsF (2.5 equiv), CuI (1 equiv)	DMF, 180 °C, 8 h		42 (isol.), 45 (GC and NMR)	82
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ K (1.2 equiv), CuI (1 equiv)	DMF, 45 °C, 8 h		52 (isol.)	224
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 120 °C, 8 h		70 (isol.)	267
	Copper anode, CF ₃ Br (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		98 (GC)	206
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		32 (isol.), 39 (GC)	292
	CF ₃ SiMe ₃ (1 equiv), CuI (1.1 equiv), KF (1.1 equiv)	DMF/NMP (1 : 1), 25 °C, 6 h		28 (isol.), 34 (GC)	292
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		34 (GC)	216
	[(SiMe ₃) ₂ Cu][(CF ₃) ₂ Cu]	ArBr (10 equiv), Benzene/DMI (5 : 1), 50 °C, 28 h		77 (¹⁹ F NMR)	170
	CF ₃ I (11 equiv), Cu (20 equiv)	HMPA, 110 °C, 40 h		42 (isol.)	190

Table 3. Continued

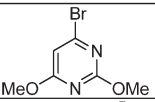
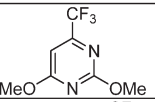
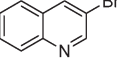
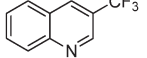
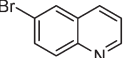
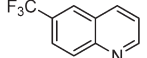
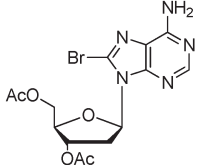
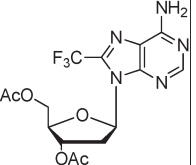
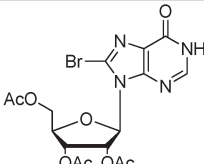
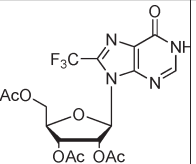
Aryl Bromide	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	CF ₃ I (15 equiv), Cu (29 equiv)	HMPA, 125 °C, 40 h		31 (isol.)	190
	CF ₃ I (3.7 equiv), Cu (8.1 equiv)	HMPA, 130–140 °C, 20 h		74 (isol.)	189
	CF ₃ Br (6 equiv), Cu (4 equiv)	HMPA, 130 °C, 20 h		22 (isol.)	204
	Copper anode, CF ₃ Br, (excess)	tmeda (4 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, r. t. to 95 °C, 2 h		98 (GC)	206
	CF ₃ I (7.4 equiv), Cu (5.9 equiv)	DMF, 140 °C, 24 h		28 (isol.)	189
	CF ₃ I (20 equiv), Cu (35 equiv)	HMPA, 45 °C, 24 h		64 (isol.)	190
	CF ₃ I (25 equiv), Cu (39 equiv)	HMPA, 45 °C, 24 h		42 (isol.)	190

Table 4. Copper-Promoted Trifluoromethylation Reactions of Aryl Chlorides





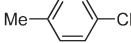

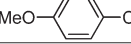
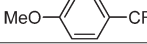


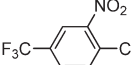
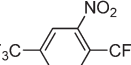

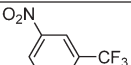
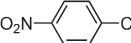
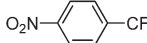
Aryl Chloride	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 120 °C, 8 h		52 (isol.)	267
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 120 °C, 8 h		32 (isol.)	267
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 120 °C, 8 h		34 (isol.)	267
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 120 °C, 8 h		37 (isol.)	267
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		59 (GC)	207a
	Cu (6 equiv), CF ₂ Br ₂ (2 equiv)	DMAC, 100 °C, 4 h, charcoal		89 (GC)	208
	Cu (6 equiv), CF ₂ Br ₂ (2 equiv)	DMAC, 100 °C, 4 h, charcoal		98 (GC)	208
	CICF ₂ CO ₂ Me (2 equiv), CuI (1 equiv), KF (1 equiv)	DMF, 100–110 °C, 10 h		70 (isol.)	98b
	BrCF ₂ CO ₂ Me (2 equiv), CuI (1 equiv), KF (1 equiv)	DMF, 90 °C, 8 h		68 (isol.)	98b
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 120 °C, 8 h		72 (isol.)	267
	CF ₃ I (6 equiv), Cu (8 equiv)	HMPA, 130–140 °C, 20 h		20 (isol.)	189
	Copper anode, CF ₃ Br (excess)	1. PBu ₃ (2 equiv), Bu ₄ NBr (0.05 equiv), Current 0.3 A, DMF, –15 °C, 6 h		55 (isol.)	206

Table 4. Continued

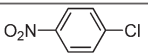

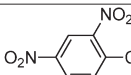
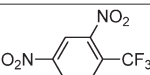
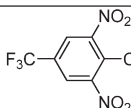
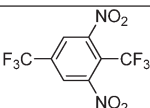
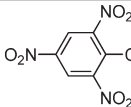
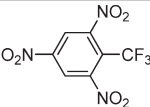
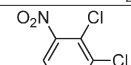
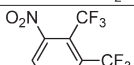
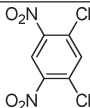
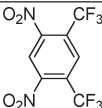

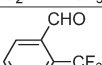
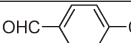
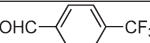
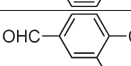
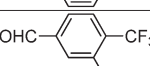

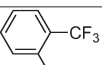
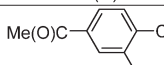
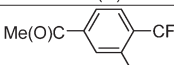
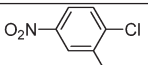
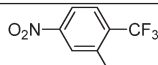

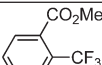
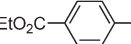
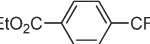

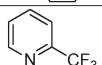

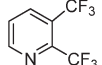
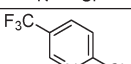
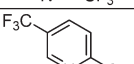
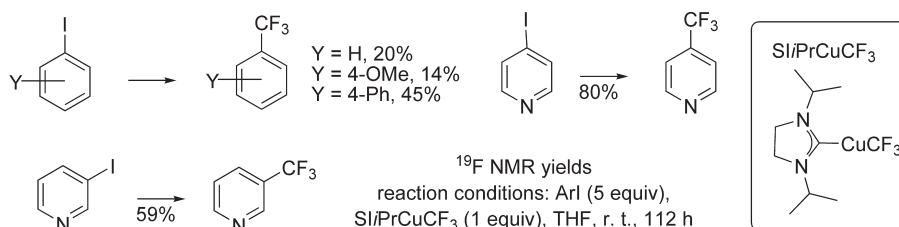
Aryl Chloride	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
		2. ArI, DMF, 90 °C, 3 h			
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 120 °C, 8 h		67 (isol.)	267
	ClCF ₂ CO ₂ Me (2 equiv), CuI (1 equiv), KF (1 equiv)	DMF, 100–110 °C, 10 h		18 (isol.)	98b
	BrCF ₂ CO ₂ Me (2 equiv), CuI (1 equiv), KF (1 equiv)	DMF, 90 °C, 10 h		15 (isol.)	98b
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 4 h		93 (GC)	207a
	Cu (6 equiv), CF ₂ Br ₂ (2 equiv)	DMAC, 100 °C, 2 h, charcoal		87 (GC)	208
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ K (1.2 equiv), CuI (1 equiv)	DMF, 45 °C, 8 h		55 (isol.)	224
	Zn(CF ₃)Br·DMF (1 equiv), CuBr (2 equiv)	1. DMF, r. t., 3 h 2. Addition of ArI, 85–90 °C, 8 h		51 (isol.)	114
	ClCF ₂ CO ₂ Me (2 equiv), CuI (1 equiv), KF (1 equiv)	DMF, 100–110 °C, 8 h		86 (isol.)	98b
	BrCF ₂ CO ₂ Me (2 equiv), CuI (1 equiv), KF (1 equiv)	DMF, 90 °C, 9 h		75 (isol.)	98b
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 30 min		83 (GC)	207a
	ClCF ₂ CO ₂ Me (2 equiv), CuI (1 equiv), KF (1 equiv)	DMF, 100–110 °C, 7 h		90 (isol.)	98b
	BrCF ₂ CO ₂ Me (2 equiv), CuI (1 equiv), KF (1 equiv)	HMPA, 90 °C, 8 h		90 (isol.)	98b
	ClCF ₂ CO ₂ Me (2 equiv), CuI (1 equiv), KF (1 equiv)	DMF, 100–110 °C, 7 h		90 (isol.)	98b
	BrCF ₂ CO ₂ Me (2 equiv), CuI (1 equiv), KF (1 equiv)	DMF, 90 °C, 8 h		92 (isol.)	98b
	Cu (6 equiv), CF ₂ Br ₂ (2 equiv)	DMAC, 100 °C, 2 h, charcoal		100 (GC)	208
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		63 (GC)	207b
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		16 (GC)	207b
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 120 °C, 8 h		56 (isol.)	267
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		100 (GC)	207b
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		38 (GC)	207b
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		95 (GC)	207b
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		47 (GC)	207a
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		17 (GC)	207a
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 120 °C, 8 h		52 (isol.)	267
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		13 (GC)	207a
	FSO ₂ CF ₂ CF ₂ OCF ₂ CO ₂ Me (1 equiv), CuI (1 equiv)	DMF, 120 °C, 8 h		64 (isol.)	267
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		19 (GC)	207b
	CF ₃ CO ₂ Na (4 equiv), CuI (2 equiv)	NMP, 160 °C, 4 h		27 (GC)	216

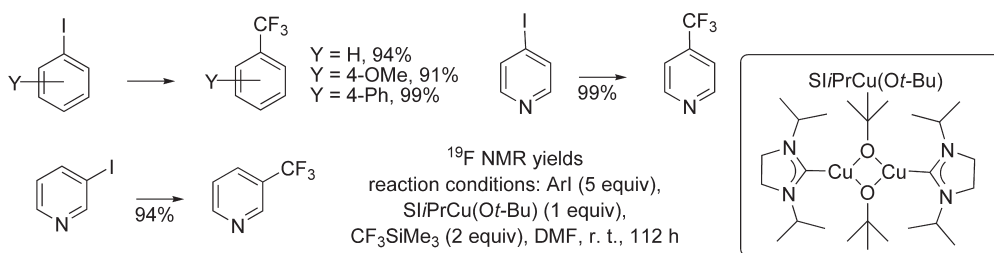
Table 4. Continued

Aryl Chloride	Trifluoromethylating Reagent	Reaction Conditions	Product	Yield, %	Ref.
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		93 (GC)	207b
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		48 (GC)	207a
	Cu (6 equiv), CF ₂ Br ₂ (2 equiv)	DMAC, 100 °C, 8 h, charcoal		45 (GC)	208
	Cu, CF ₂ Br ₂	DMAC, 100 °C, 8 h		46 (GC)	207a
	CF ₃ I (4.2 equiv), Cu (6.4 equiv)	DMF, 120–130 °C, 24 h		10 (isol.)	189
	CF ₃ I (8.5 equiv), Cu (7.8 equiv)	DMF, 140 °C, 36 h		11 (isol.)	189
	CF ₃ I (3.2 equiv), Cu (2.9 equiv)	DMF, 135–140 °C, 20 h		30 (isol.)	189

Scheme 34



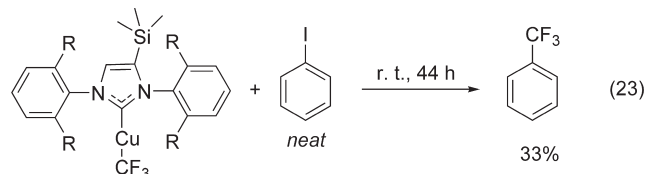
Scheme 35



Saturated NHC-stabilized CuCF₃ complex [(SiPr)Cu(CF₃)]⁶⁰ has also been shown to trifluoromethylate iodoarenes. Although quite low in THF (Scheme 34), the yields are excellent in DMF, where the reactive complex is generated in situ from its *t*-BuOCu precursor (Scheme 35).

The bulkier NHC analogue [(SiMes)Cu(CF₃)] exhibits similar reactivity toward iodoarenes (Scheme 36).¹⁷⁰ In solution this complex equilibrates with its cuprate form [(SiMes)₂Cu]⁺[Cu(CF₃)₂][−] (see section 3.3).

Most recently, the same group¹⁰¹ prepared NHC-stabilized Cu(I) fluoroacetates [(SiPr)Cu(CF₃CO₂)], [(SiPr)Cu(CF₂ClCO₂)], and [(SiMes)Cu(CF₃CO₂)]. Decarboxylation of these

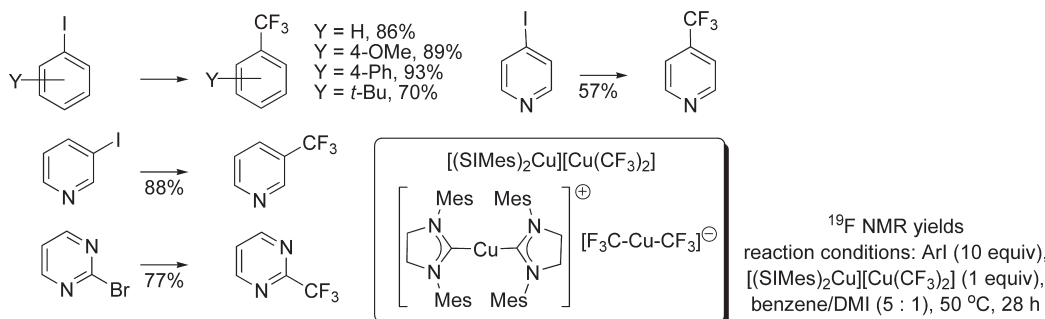


complexes at 160 °C in neat iodobenzene, 4-bromotoluene, or their solutions in DMAC gave the corresponding trifluoromethylated products in low to moderate yield (Scheme 37).

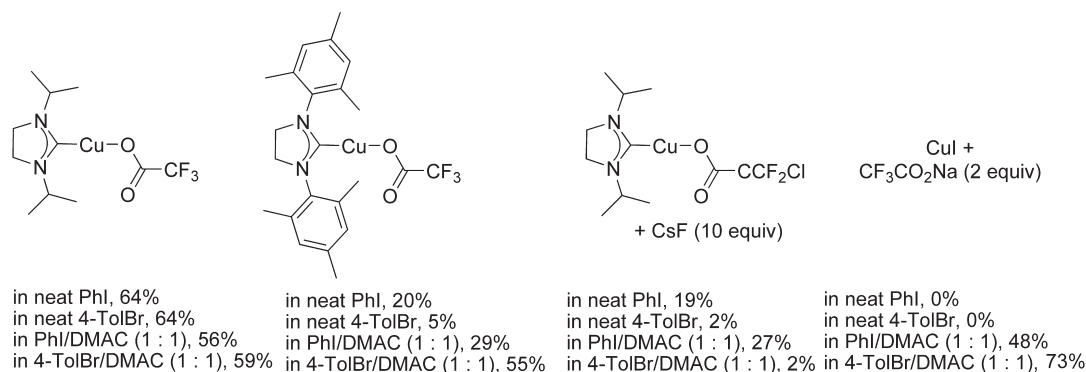
4.2. Ar–CF₃ Bond Formation at Palladium and Nickel Centers

Just 5 years ago a chemist would laugh at the idea of Pd-catalyzed nucleophilic trifluoromethylation of aryl halides. Indeed, any plausible catalytic loop for such transformation (e.g., Scheme 38)⁶⁶ would inevitably involve Ar–CF₃ reductive elimination^{59,135} as a key step. Until recently, this step was considered hopeless because of the exceptional strength and inertness of late transition metal bonds to perfluoroalkyls.^{47,48} Indeed, [(dppbz)Pd(2-Tol)(CF₃)] has been found to remain intact at 130 °C for days.¹⁷⁵ Both [(dppe)Pd(Ph)(CF₃)] and [(dppp)Pd(Ph)(CF₃)] have been reported¹³⁵ to produce PhCF₃ but only in 10–60% yield after long hours at 145 °C. For comparison, Ar–CH₃ reductive elimination from analogous nonfluorinated complexes easily occurs at 15–40 °C.³²⁶ Although the thermal

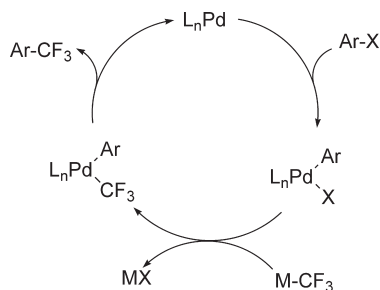
Scheme 36



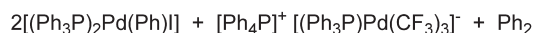
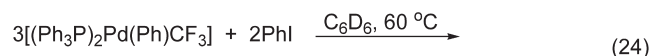
Scheme 37



Scheme 38

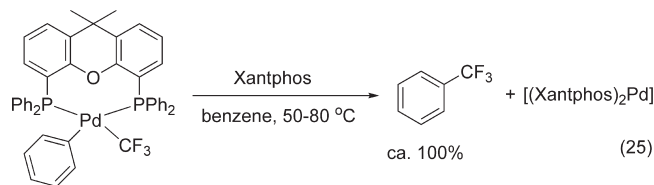


decomposition of $[(\text{Ph}_3\text{P})_2\text{Pd}(\text{Ph})(\text{CF}_3)]$ is facile, readily occurring at 60 °C in benzene in the presence of PhI, no Ph-CF₃ bond formation takes place.⁵⁹ Instead, Ph-PPh₃ reductive elimination initiates the reaction that eventually leads to a 2:1:1 mixture of $[(\text{Ph}_3\text{P})_2\text{Pd}(\text{Ph})\text{I}]$, $[\text{Ph}_4\text{P}]^+[(\text{Ph}_3\text{P})\text{Pd}(\text{CF}_3)_3]^-$, and Ph₂ (eq 24). A plausible mechanism for this complex yet highly selective transformation is shown in Scheme 39.⁵⁹



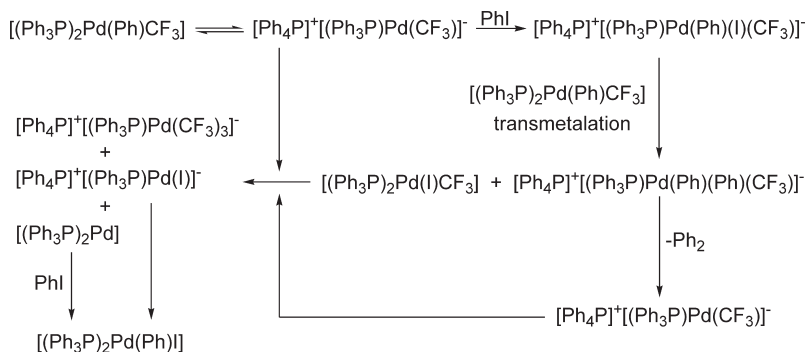
A breakthrough in the area was reported in 2006. It was found⁵⁹ that unlike numerous other trifluoromethyl palladium aryls, $[(\text{Xantphos})\text{Pd}(\text{Ph})(\text{CF}_3)]$ underwent remarkably clean and facile Ph-CF₃ reductive elimination at as low as 50–80 °C (eq 25). This result demonstrated, for the first time, the very possibility of Pd-catalyzed nucleophilic aromatic trifluoromethylation. Such catalytic process that was

reported⁶³ most recently is discussed in section 5. In that work, Ar-CF₃ reductive elimination was studied from two $[(\text{BrettPhos})\text{Pd}(\text{Ar})(\text{CF}_3)]$ complexes, as shown in eq 26 (see also eq 18). In both cases Ar-CF₃ bond formation cleanly occurred in dioxane at 80 °C to follow first-order decay with $t_{1/2} = 22\text{--}24$ min, indicating that the reaction rate was independent of the substituents on the σ -aryl ligand. This unexpected result was rationalized by DFT calculations. The computational study predicted nearly identical activation barriers of ca. 22 kcal mol^{−1} for both complexes due to significant elongation of the strong Pd-CF₃ bond in the transition state being by far the major contributor to the activation energy. As the substituent on the σ -aryl ligand has little influence on the Pd-CF₃ bond strength, Ar-CF₃ reductive elimination from both complexes occurred at similar rates.

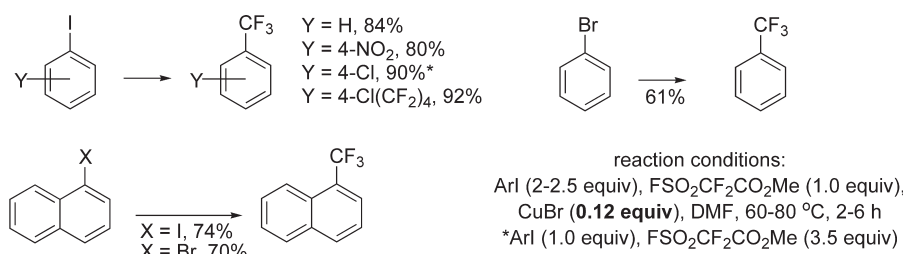


Also very recently, Ar-CF₃ reductive elimination from Pd(IV) complexes was reported.^{176,178} Quite expectedly,^{135,178} a series of Pd(II) complexes $[(\text{L}-\text{L})\text{Pd}(\text{Ar})(\text{CF}_3)]$ (L-L = *t*-Bu-bpy, tmeda, dppe) have been found¹⁷⁶ unreactive toward Ar-CF₃ reductive elimination, even under drastic conditions. In the presence of *N*-fluoro-2,4,6-collidinium triflate, however, clean formation of the Ar-CF₃ bond occurred at 80 °C in nitrobenzene to give the coupling products in 29–89% yield. In one case, an intermediate Pd(IV) complex $[(t\text{-Bu-bpy})\text{Pd}(\text{CF}_3)(\text{F})(\text{OTf})(4\text{-C}_6\text{H}_4\text{F})]$

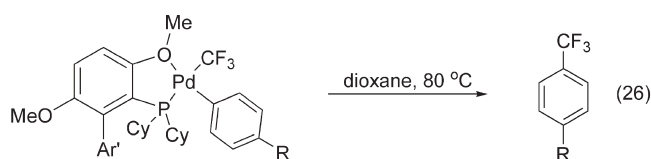
Scheme 39



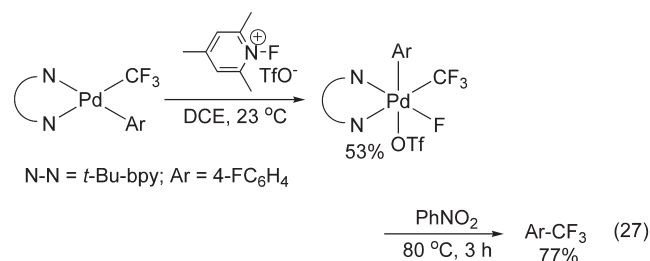
Scheme 40



was isolated, structurally characterized (section 3.4), and shown to reductively eliminate 4-fluorobenzotrifluoride (eq 27). Although quite interesting, these Pd(II)/Pd(IV) transformations are unrelated to the ultimate goal of trifluoromethylation (and functionalization in general) of haloarenes because, unlike Pd(0), neither Pd(II) nor Pd(IV) can activate aromatic carbon–halogen bonds. Another CF₃Pd(IV) complex, [(bzq)Pd(CF₃)(OAc)₂(OH₂)], has been found¹⁷⁸ to undergo reductive elimination at 60 °C to produce bzq–CF₃, bzq–OAc, and bzq–OH. In acetic acid, 1,2-dichloroethane, chloroform, and nitrobenzene, the bzq–CF₃ bond formation (54–62%) was predominant. However, in 1,2-dichloroethane containing 50 equiv of pyridine, bzq–OH was formed in 84% yield. Mechanistic studies pointed to Pd–OAc bond ionization prior to Ar–CF₃ reductive elimination.



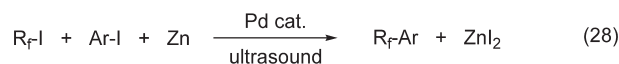
Ar' = 2,4,6-*i*-Pr₃C₆H₂; R = CO₂Me, OMe



Trifluoromethyl nickel aryls [(dippe)Ni(Ar)(CF₃)] readily decompose in solution to give biaryls, [(dippe)Ni(CF₃)₂], and no ArCF₃.¹⁸⁸ The latter formed, albeit in only 11–22% yield, when the decomposition was carried out in the presence of PhZnBr, ZnBr₂, or water as promoters.

5. METAL-CATALYZED AROMATIC TRIFLUOROMETHYLATION REACTIONS

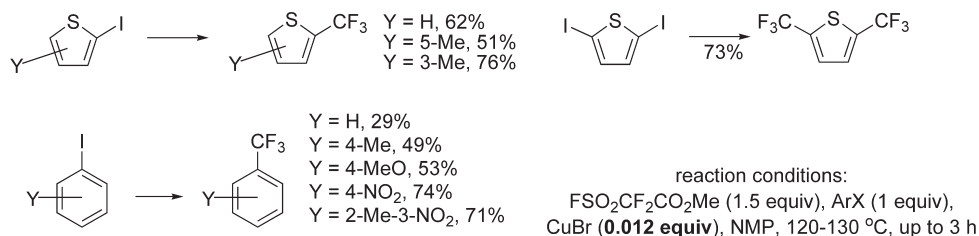
Aromatic trifluoromethylation reactions that are catalytic in metal are still rare. In 1982, Kitazume and Ishikawa³²⁷ briefly communicated Pd-catalyzed reductive coupling of perfluoroalkyl iodides with various organic halides (iodoarenes included) in the presence of Zn dust under sonication (eq 28). No full report has followed. Interestingly, although [(Ph₃P)₂Pd(Cl)₂] was reported³²⁷ to be active added catalyst, more recently it was demonstrated⁵⁹ that Ph₃P-stabilized trifluoromethyl Pd aryls do not undergo Ar–CF₃ reductive elimination (see eq 24 and Scheme 39 in section 4.2).



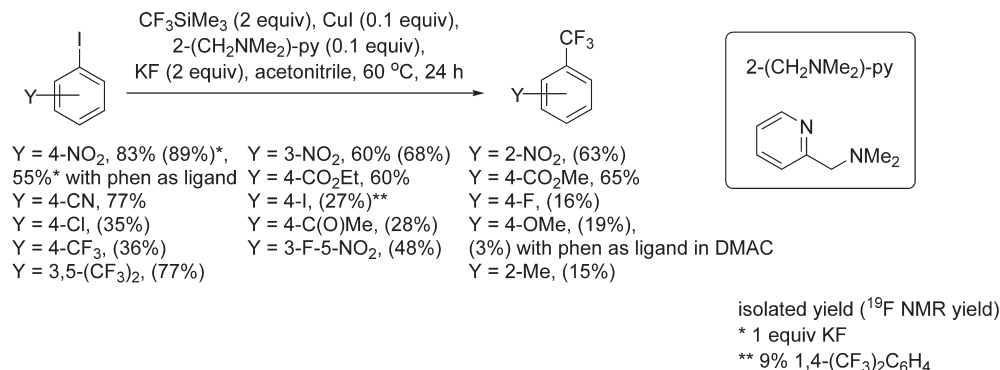
In 1989, Chen and Wu¹⁰⁰ reported trifluoromethylation of aryl, alkenyl, and alkyl halides with FSO₂CF₂CO₂Me in the presence of CuI in catalytic quantities (12 mol %). The reaction with ArX proceeds in DMF or DMSO at as low as 60–80 °C to furnish the corresponding benzotrifluorides in 61–92% yield (Scheme 40).

Nine years after Chen and Wu published their report,¹⁰⁰ a patent³²⁸ appeared describing applications of a similar catalytic system with only 1.2 mol % Cu. As described in the patent, it is essential to replace DMF with NMP and CuI with CuBr in order to achieve good solubility of Cu(I) in the reaction medium

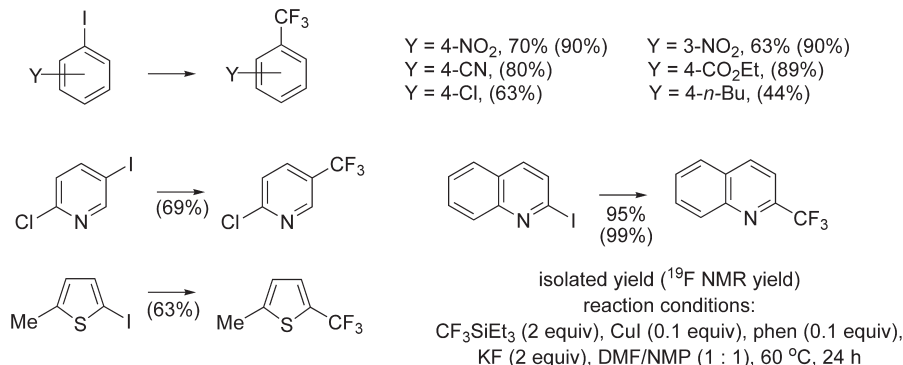
Scheme 41



Scheme 42



Scheme 43



(Scheme 41). This explanation is only partially satisfactory, because as the reaction occurs, large quantities of iodide are released that may bind to the Cu(I).

Considering the reported possibility of performing the trifluoromethylation with FSO₂CF₂CO₂Me in a catalytic manner,^{100,328} it is surprising that in numerous other papers^{226–243} and patents^{210,221,244–263} using this method a Cu(I) salt is employed in stoichiometric rather than catalytic amounts.

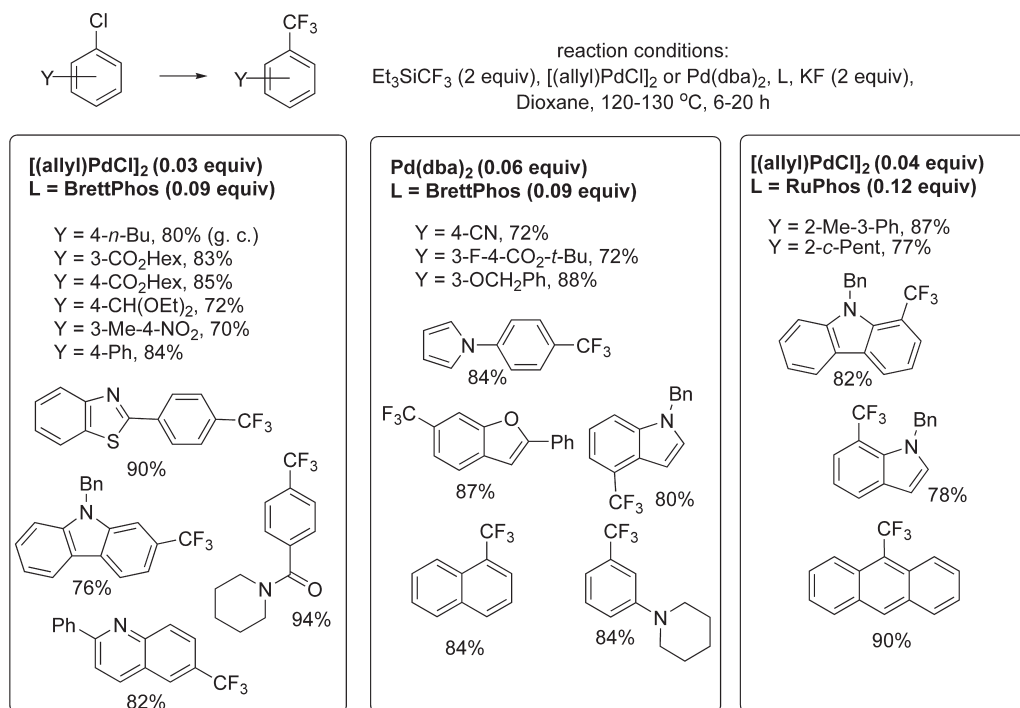
Two Japanese groups very recently developed Cu-catalyzed aromatic trifluoromethylation reactions with CF₃SiR₃ (R = Me or Et). Inoue et al.⁶¹ describe in their 2009 Japanese patent (filed in March 2008) a series of Cu-catalyzed aromatic trifluoromethylation reactions with Ruppert's reagent. Oishi, Kondo, and Amii⁶² reported a similar Cu-catalyzed process with CF₃SiEt₃ in a 2009 communication (submitted in December 2008).

The protocol developed by Inoue's group⁶¹ employs 10 mol % of CuI and 2-(*N,N*-dimethylaminomethyl)pyridine as a ligand

(Scheme 42). The CuI/phen-based catalytic system is less efficient under these conditions. Good yields can be obtained for electron-deficient iodoarene substrates, whereas the trifluoromethylation of 2-iodotoluene and 4-iodoanisole affords the corresponding products in only 15–19% yield. Interestingly and importantly, recyclable acetonitrile is the best solvent for the reaction; the yields do not improve in DMAC which is a more typical solvent for aromatic trifluoromethylation with CF₃Cu species.

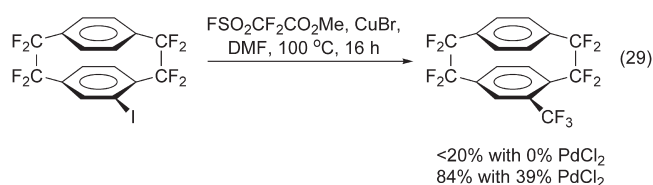
The Oishi–Kondo–Amii catalytic method⁶² employs more readily available and affordable 1,10-phenanthroline as a ligand but much more expensive CF₃SiEt₃ as the trifluoromethyl source (Scheme 43). The original Urata–Fuchikami protocol²⁹¹ (Scheme 29) requires stoichiometric amounts of Cu(I). It was reasoned⁶² that stoichiometric quantities of copper are needed because of the significant difference in rates of the two key steps. While the generation of reactive CuCF₃ from CF₃SiEt₃, KF, and

Scheme 44



Cu(I) is fast, the subsequent coupling with ArX and regeneration of Cu(I) is much slower. As a result, insufficient quantities of Cu(I) are supplied to regenerate CuCF_3 , thereby leaving the trifluoromethyl source to undergo rapid fluoride-induced decomposition to difluorocarbene. Moreover, slow consumption of CuCF_3 in the coupling process leads to its loss to side reactions. The role of phanthroline is therefore believed⁶² to be twofold: (i) it speeds up the Ar- CF_3 coupling, thus providing sufficient quantities of $[(\text{phen})\text{CuI}]$ for CF_3 transfer from Si to Cu and (ii) the ligand likely stabilizes the CuCF_3 species toward side reactions. The catalytic reaction proceeds smoothly with iodoarenes bearing electron-withdrawing groups, iodopyridines, and 2-iodoquinoline. The only nonactivated iodoarene used in this reaction, 4-*n*-Bu $\text{C}_6\text{H}_4\text{I}$, underwent trifluoromethylation in a lower yield (44%).

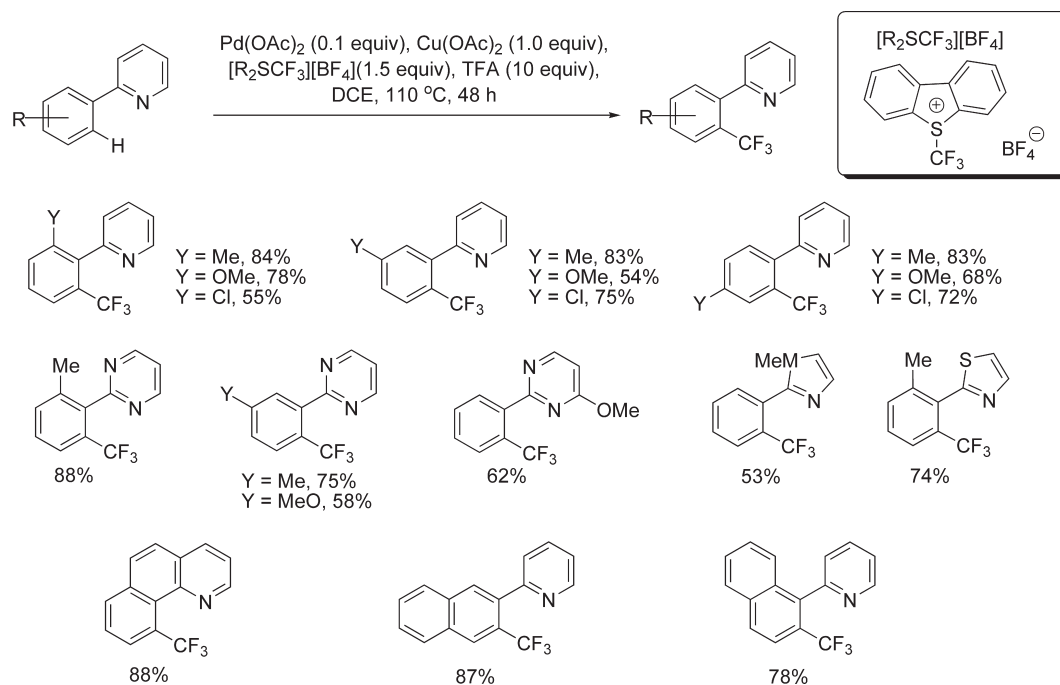
In 1999–2000, Roche and Dolbier^{329,330} reported an intriguing observation of the beneficial effect of *catalytic* amounts of PdCl_2 on the trifluoromethylation of iodinated 1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes with $\text{FSO}_2\text{CF}_2\text{CO}_2\text{Me}-\text{CuBr}$ in DMF (e.g., eq 29). In the absence of PdCl_2 , the reaction was poorly selective, leading mostly to deiodination and only <20% of the trifluoromethylated product. However, when PdCl_2 was added (ca. 40 mol %) the desired compound was obtained in 84% yield.³²⁹ The same effect of PdCl_2 , yet in much smaller amounts (ca. 5 mol %), was then observed in the double trifluoromethylation reaction of diiodo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes.³³⁰



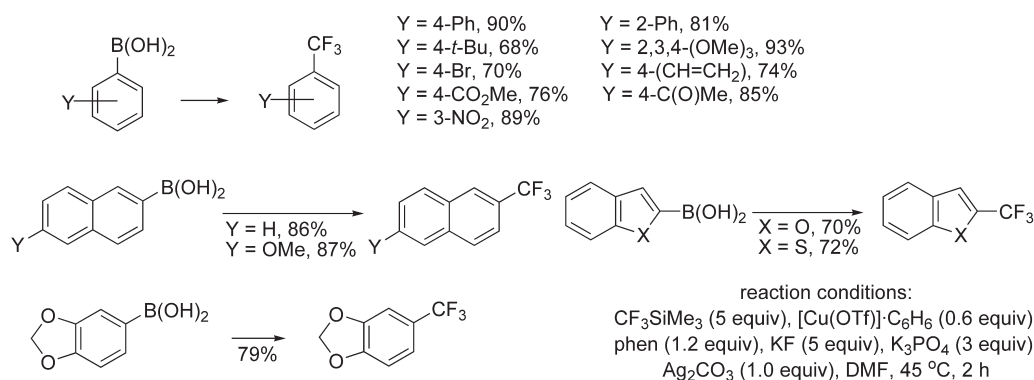
Since the original Roche–Dolbier reports,^{329,330} similar observations of Pd catalysis have also been made by Qing³³¹ and more recently by Liu and Chen^{264,265} for trifluoromethylation of bromoalkenes and bromoporphyrins with CuCF_3 . The mechanism of action of the Pd additives in these reactions^{264,265,329–331} is unclear. Considering the exceptional reluctance of most trifluoromethyl Pd(II) aryls to undergo Ar- CF_3 reductive elimination (see section 4.2), we believe that in reaction 27 and similar processes^{264,265,329–331} the role of Pd is limited to Ar-X bond activation via oxidative addition. Aryl transfer from Pd to the Cu atom already bearing a CF_3 group followed by Ar- CF_3 coupling at the copper center would conclude the transformation. An alternative mechanism involving transmetalation of the CF_3 group to an iodo Pd aryl intermediate perhaps cannot be completely ruled out as the large steric bulk of the σ -aryl on Pd might lower the activation barrier for Ar- CF_3 reductive elimination. However, $[(\text{dppbz})\text{Pd}(2\text{-Tol})(\text{CF}_3)]$ bearing a bulky *o*-tolyl does not undergo Ar- CF_3 reductive elimination even when heated at 130 °C for days¹⁷⁵ (see section 4.2).

After the principle feasibility of clean Ar- CF_3 reductive elimination from Pd(II) was demonstrated,⁵⁹ Buchwald et al.⁶³ most recently developed the first Pd-catalyzed trifluoromethylation of chloroarenes (Scheme 44). Aryl bromides and triflates also reacted, although the yields were lower. The key to success is the BrettPhos ligand that has proven to be remarkably efficient in a number of otherwise unattainable Pd-catalyzed transformations.³³² The method⁶³ is applicable to both electron-deficient and electron-enriched aryl chlorides and exhibits good tolerance for functional groups and some heteroaromatic rings. It is unclear, however, if this catalytic reaction is efficient with substrates that can coordinate to Pd, such as 2,6-unsubstituted halopyridines, 2-unsubstituted quinolines, etc.

Scheme 45



Scheme 46

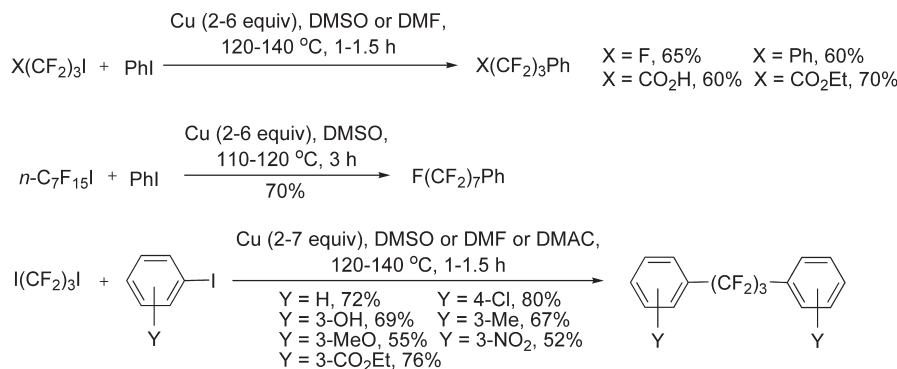


Wang, Truesdale, and Yu⁶⁴ have recently reported an interesting example of Pd-catalyzed *electrophilic* aromatic trifluoromethylation with (trifluoromethyl)dibenzothiophenium triflate or tetrafluoroborate (Scheme 45). The reaction furnishes ortho-trifluoromethylated aromatic compounds that are formed via cyclopalladation. The scope of substrates is limited to arenes that (i) have at least one ortho C–H bond, (ii) are devoid of strong electron-withdrawing substituents, and (iii) bear a directing group for coordination to Pd prior to cyclometalation. The process uses $\text{Pd}(\text{OAc})_2$ (10%), an equimolar amount of $\text{Cu}(\text{OAc})_2$, and 10 equiv of trifluoroacetic acid, in the absence of which the reaction does not proceed. A mechanistic study¹⁷⁸ on C–CF₃ reductive elimination from related $[(\text{bzq})\text{Pd}(\text{CF}_3)(\text{OAc})_2(\text{OH}_2)]$ (section 4.2) suggests that the $\text{Cu}(\text{OAc})_2$ and CF_3COOH additives (i) serve as a source of AcOH that is needed to oxidize the originally produced

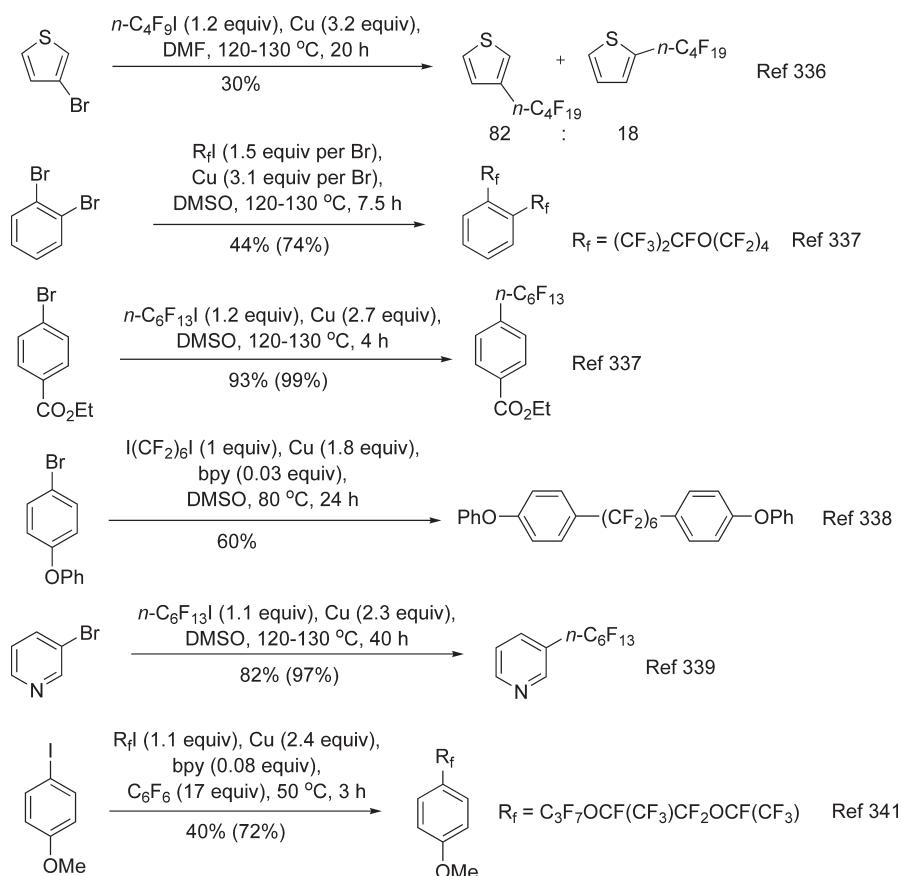
cyclopalladated dimer to the key mononuclear $\text{CF}_3\text{Pd}(\text{IV})$ intermediate and (ii) may also improve the yield by scavenging reactive Pd species generated in the C–CF₃ coupling step.

Also very recently, trifluoromethylation of arylboronic acids was reported.³³³ The reaction employs 1,10-phenanthroline-stabilized CuCF_3 generated in situ from CF_3SiMe_3 , KF, and $[\text{Cu}(\text{OTf})]\cdot\text{C}_6\text{H}_6$ (Scheme 46). A stoichiometric amount of Ag_2CO_3 is required to oxidize trifluoromethyl Cu(I) aryl intermediates after aryl transfer from boron prior to Ar–CF₃ coupling. Although this reaction proceeds under mild conditions (45 °C) and uses only semicatalytic quantities of Cu(I) (0.6 equiv), a 5-fold excess of Ruppert's reagent is needed. Not surprisingly, in contrast with coupling reactions of CuCF_3 species with aryl halides, electron-enriched arylboronic acids gave slightly better yields than those bearing electron-withdrawing substituents.

Scheme 47



Scheme 48



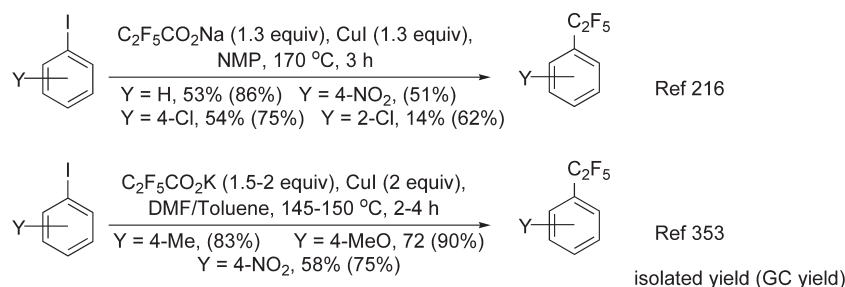
isolated yield (GC yield)

6. AROMATIC PERFLUOROALKYLATION WITH HIGHER R_f

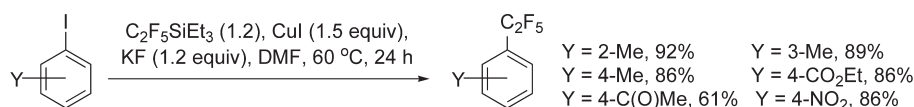
As described in the Introduction (section 1), trifluoromethylated molecules find their main uses in the synthesis of biologically active compounds, such as agrochemicals and pharmaceuticals. Compounds bearing longer perfluoroalkyl chains are more widely employed as building blocks for materials, polymers, elastomers, surfactants, and in various branches of fluorine chemistry.³³⁴ Many of the Cu-mediated trifluoromethylation reactions described above can be extended to the

introduction of higher R_f groups into the aromatic ring. The most general and widely used method is perfluoroalkylation with R_fCu reagents generated in situ from perfluoroalkyl iodides and copper. Pentafluoroethylation can also be achieved via decarboxylation of sodium or methyl perfluoropropionate in the presence of Cu(I) or via C₂F₅ transfer from C₂F₅SiMe₃ to copper. These methods afford individual perfluoroalkylarenes. On the other hand, trifluoromethylation with CuCF₃ at elevated temperatures is often accompanied by a side pentafluoroethylation reaction because of the in situ formation of CuC₂F₅ via α-F-elimination

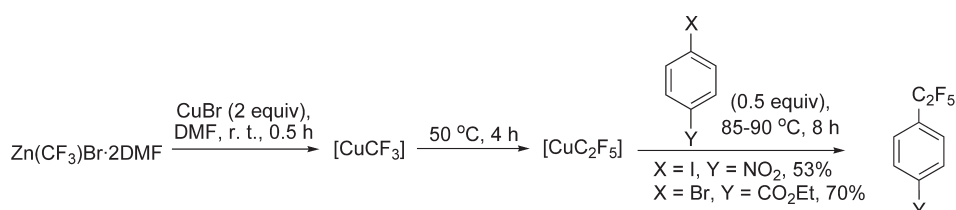
Scheme 49



Scheme 50



Scheme 51



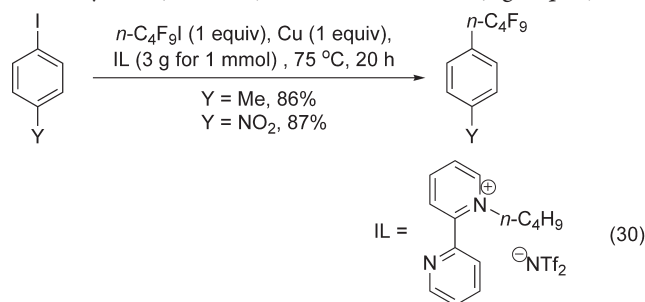
and CF_2 insertion into the $\text{Cu}-\text{CF}_3$ bond. In several cases the formation of mixtures of $\text{CF}_3(\text{CF}_2)_n\text{Cu}$ ($n > 0$) is the main reaction pathway that eventually leads to a mixture of aromatic products bearing different R_f substituents. Sometimes this process of elongation of the perfluoroalkyl chain can be controlled. For instance, $\text{Cd}(\text{CF}_3)\text{X}^{167}$ and $\text{Zn}(\text{CF}_3)\text{Br} \cdot 2\text{DMF}^{114}$ have been converted exclusively to CuC_2F_5 . Double CF_2 insertion into the $\text{Cu}-\text{C}$ bond of $\text{C}_6\text{F}_5\text{Cu}$ has been shown^{286,335} to give $\text{C}_6\text{F}_5\text{CF}_2\text{CF}_2\text{Cu}$.

A large number of perfluoroalkylation reactions with various R_fI are described by McLoughlin and Thrower in their original 1969 report,⁵⁶ including $n\text{-C}_n\text{F}_{2n+1}\text{I}$ ($n = 2, 5, 7, 9$), α,ω -diiodides $\text{I}(\text{CF}_2)_n\text{I}$ ($n = 2, 3, 4, 7$), $\text{I}(\text{CF}_2)_3\text{X}$ ($\text{X} = \text{Ph}, \text{COOEt}, \text{COOH}$), and $i\text{-C}_3\text{F}_7\text{I}$. Selected typical examples are presented in Scheme 47.

Following this methodology, numerous similar transformations have been reported (e.g., Scheme 48), including coupling of (i) bromo- and iodothiophenes with $\text{CF}_3(\text{CF}_2)_n\text{I}$ ($n = 0, 3, 4, 7$);³³⁶ (ii) bromo- and dibromoarenes with $\text{CF}_3(\text{CF}_2)_n\text{I}$ ($n = 5, 7$) and $\text{FC}(\text{CF}_3)_2\text{O}(\text{CF}_2)_n\text{I}$ ($n = 4, 8$);^{337,338} (iii) bromo- and dibromopyridines, -pyrimidines, and -furans with $n\text{-C}_6\text{F}_{13}\text{I}$;³³⁹ (iv) iodoarenes with $n\text{-C}_8\text{F}_{17}\text{I}$ and $n\text{-C}_8\text{F}_{17}\text{OCF}_2\text{I}$;³⁴⁰ and (v) iodoarenes with secondary iodides $n\text{-C}_3\text{F}_7\text{O}[\text{CF}(\text{CF}_3)\text{CF}_2\text{O}]_n\text{CF}(\text{CF}_3)\text{I}$ ($n = 1, 2$).³⁴¹ Interestingly, the best yields in the latter case were obtained not in DMSO or DMF but in C_6F_6 with 4 equiv of DMSO and 0.07 equiv of bpy which speeded up the reaction considerably. Since this beneficial effect of bpy was first observed³³⁸ it has been widely used in many perfluoroalkylation reactions of aryl halides.^{342–351}

A novel ionic liquid, 1-butyl-2,2'-bipyridinium bis(trifluoromethanesulfonyl)amide, has been used as a recyclable medium

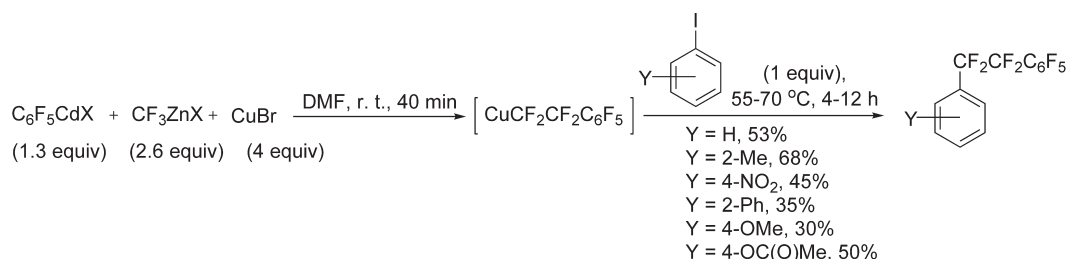
for cross-coupling of aryl iodides with perfluoroalkyl iodides in the presence of Cu under mild conditions (75 °C).³⁵² Excellent isolated yields (85–91%) have been obtained (e.g., eq 30).



Sodium and potassium perfluoropropionates in the presence of CuI have been used^{216,353} for pentafluoroethylation of aryl halides. Temperatures up to 170 °C are required for the decarboxylation to proceed and the yields are in general lower than in similar trifluoromethylation reactions using sodium trifluoroacetate (Scheme 49). Heptafluoropropylbenzene has been obtained from iodobenzene and perfluorobutylate, albeit in only 30% yield. There has been one example of pentafluoroethylation with methyl perfluoropropionate.⁸² The reaction with iodobenzene occurs in sulfolane at 180 °C to yield 50% of the desired product after 8 h.

Reactions of $\text{ClCF}_2\text{CO}_2\text{Me}$ or $\text{BrCF}_2\text{CO}_2\text{Me}$ with PhX ($\text{X} = \text{I}, \text{Br}$) in the presence of KF and catalytic quantities of CuI have been reported³⁵⁴ to produce mixtures of perfluoroalkylbenzenes $\text{CF}_3(\text{CF}_2)_n\text{Ph}$, predominantly with $n = 0, 1, 2$.

Scheme 52



However, benzotrifluoride ($n = 0$) becomes the main product when CuI is used in stoichiometric amounts under similar conditions.

Pentafluoroethylation of iodoarenes has been performed with $\text{C}_2\text{F}_5\text{SiMe}_3$ (Scheme 50).²⁹¹ There has also been one example of use of $n\text{-C}_3\text{F}_7\text{SiMe}_3$ to obtain 1-perfluoropropyl-4-nitrobenzene in 41% yield from 4-iodonitrobenzene.

Heating CF_2Br_2 or CF_2BrCl with Cu powder in DMF leads to mixtures of perfluoroalkyl copper reagents $\text{CF}_3(\text{CF}_2)_n\text{Cu}$ with n up to 16, the major products being perfluoroethyl-, propyl- and butylcopper species.³⁵⁵ The distribution can be controlled by temperature and other factors. For instance, with CF_2Br_2 at 85 °C, $n\text{-C}_4\text{F}_9\text{Cu}$ is mainly produced (ca. 80%), whereas use of CF_2BrCl at 70 °C favors the formation of $\text{C}_2\text{F}_5\text{Cu}$ with 80% selectivity. The $\text{C}_2\text{F}_5\text{Cu}$ generated this way can be used to pentafluoroethylate iodoarenes. A similar approach to perfluoroethyl aromatic compound is based on CuC_2F_5 obtained from $\text{Zn}(\text{CF}_3)\text{Br} \cdot 2\text{DMF}$ and CuBr (Scheme 51).¹¹⁴

As mentioned above, double CF_2 insertion into the Cu–C bond of $\text{C}_6\text{F}_5\text{Cu}$ leads to $\text{C}_6\text{F}_5\text{CF}_2\text{CF}_2\text{Cu}$ that has been shown^{286,335} to perfluoroalkylate iodoarenes in 30–68% yield. The $\text{C}_6\text{F}_5\text{CF}_2\text{CF}_2\text{Cu}$ reagent can be prepared from pregenerated CuCF_3 and $\text{C}_6\text{F}_5\text{Cu}$ or directly from $\text{C}_6\text{F}_5\text{CdX}$, CF_3ZnX ($\text{X} = \text{Br}$, CF_3), and CuBr (Scheme 52).

7. CONCLUSIONS AND OUTLOOK

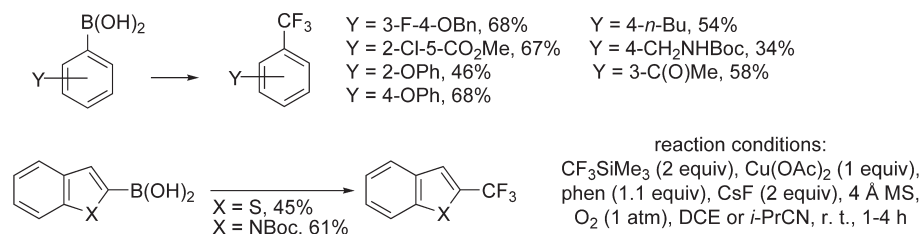
Since the discovery of the McLoughlin–Thrower reaction^{55,56} in the 1960s (eq 1), considerable progress has been made in the important, demand-driven area of metal-promoted and metal-catalyzed aromatic trifluoromethylation. A number of promising findings have been reported over the past 5 years, including the first examples of previously inconceivable $\text{Ar}-\text{CF}_3$ bond formation at Pd(II),^{59,66} followed by the most recent development of the first Pd-catalyzed trifluoromethylation of aryl chlorides.⁶³ Important advancements have also been made in the development of Cu-catalyzed trifluoromethylations^{61,62,100} and $\text{Ar}-\text{CF}_3$ bond formation with well-defined Cu(I) complexes.^{60,170} However, many efforts in the area still remain underdeveloped, and numerous improvements are desired.

With regard to the use of copper and its compounds, one of the greatest challenges is to develop promoters and conditions that would allow high-yielding trifluoromethylations of bromoarenes. Although in some cases aryl bromides can be successfully used in Cu-mediated perfluoroalkylation reactions, iodoarenes are much more preferred due to their enhanced reactivity. However, iodoarenes are less abundant and much more costly. Another problem with Cu-promoted

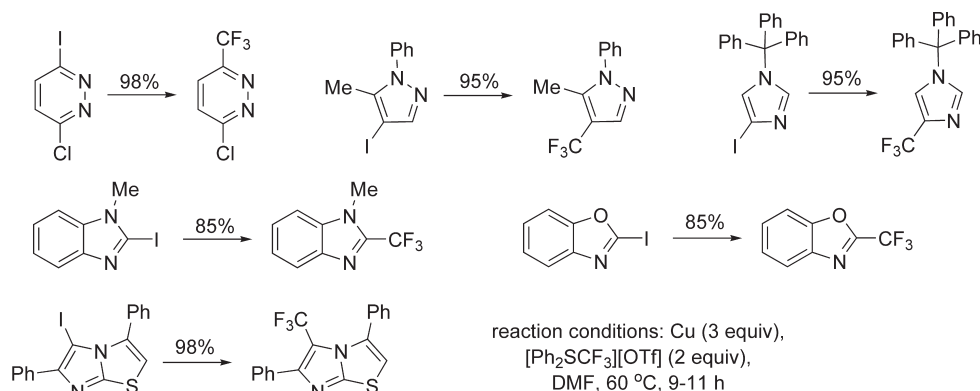
trifluoromethylations deals with the fact that most of these reactions proceed well only in aprotic dipolar solvents such as DMF, DMSO, NMP, and HMPA. Let alone more hazardous HMPA, all of these solvents are usually nonrecyclable while being expensive. Shreeve's³⁵² demonstration of successful use of a recyclable ionic liquid as a medium for the McLoughlin–Thrower reaction is an important advance. However, the problem is far from being solved. Further developments are needed toward the use of ionic liquids as well as low-cost, recyclable solvents for various trifluoromethylation reactions. As copper is relatively inexpensive, its use in stoichiometric quantities is tolerable. However, using Cu in catalytic quantities for perfluoroalkylation reactions is certainly desirable.

Palladium is incomparably more costly than copper. Therefore, a utilizable nucleophilic aromatic trifluoromethylation process based on Pd must use catalytic, minimal quantities of this precious metal. Furthermore, many ligands employed in various Pd-catalyzed reactions often cost more than the metal itself. This is the case with BrettPhos that is used in the only currently available Pd-catalyzed nucleophilic aromatic trifluoromethylation reaction. Representing a remarkable achievement, this process is likely already being used and will be used in the medicinal chemistry and discovery agrochemical laboratories. However, the current Aldrich and Strem catalogs suggest that BrettPhos might be too costly for applications on a larger scale: as of February 2011, the Aldrich price for BrettPhos is \$40.40 for 0.1 g or ca. \$217 000.00 per mol (537 g). Of course, retail prices for chemicals are considerably higher than the bulk prices. But even so, the bulk price for BrettPhos has to be $1/100$ of its current retail price to become comparable with the current Johnson-Matthey price of palladium on the U.S. market, \$2282.5 per g-atom (\$825.00 per troy oz). Therefore, for a Pd-catalyzed trifluoromethylation reaction that could be run on a larger scale, other less expensive ligands are needed. Finding such ligands is a considerable challenge. Not only must such ligands promote $\text{Ar}-\text{CF}_3$ reductive elimination, the most difficult step of the catalytic loop, but they should also be compatible with other steps within the same loop. BrettPhos obviously meets both requirements, whereas Xantphos does not. While allowing for the $\text{Ar}-\text{CF}_3$ bond formation at Pd,⁵⁹ Xantphos is easily displaced by “ CF_3^- ”, which leads to quick and irreversible catalyst deactivation. Another problem associated with the development of new ligands for Pd-catalyzed trifluoromethylation reactions is the facile transmetalation reaction between $[\text{LPd}(\text{CF}_3)(\text{Ar})]$ and $[\text{LPd}(\text{Ar})(\text{X})]$ ($\text{X} = \text{halide}$, formerly of the ArX substrate), which are produced in the first and second steps of the catalytic cycle, respectively (Scheme 38). This transmetalation is facile, leading to

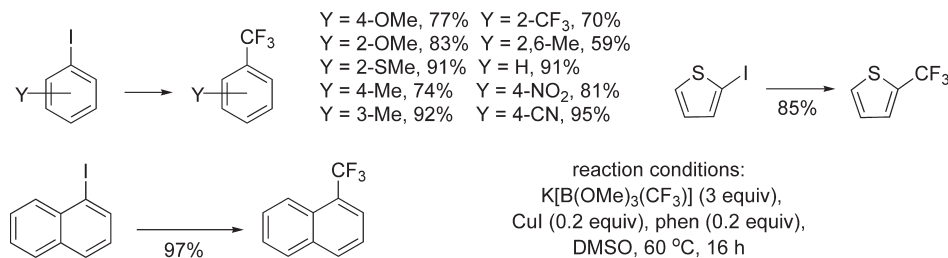
Scheme 53



Scheme 54



Scheme 55



$[\text{LPd}(\text{Ar})_2]$ which undergoes Ar–Ar reductive elimination, and stable $[\text{LPd}(\text{CF}_3)(\text{X})]$ that is catalytically inactive.^{59,135} Very little work has been done toward the development of Ni-catalyzed trifluoromethylation reactions.

A comment is due on CF_3 sources for trifluoromethylation reactions. The currently most popular Ruppert-type reagents are efficient, safe, easy to handle, yet expensive. A number of lower cost, potentially useful CF_3 sources (section 2) are on the Montreal Protocol list, which limits their availability for research in certain countries. While being all for safe and environmentally benign technologies, we believe that limited access to useful chemicals slows down research and, as a result, progress in many important areas, trifluoromethylation chemistry certainly being one. Scientists and engineers in both industry and academia have proven capable of handling safely and wisely highly toxic and hazardous materials, such as HCN, CO, azides, and various radioactive compounds. Banning many polyfluorinated methanes completely from the market in even strictly limited, research quantities is unlikely to eliminate the ozone layer problem. Yet, it is guaranteed to retard

developments in the vital area of aromatic trifluoromethylation targeted at finding an alternative to the environmentally unfriendly Swarts reaction, which still remains the only method to manufacture trifluoromethylated aromatics. Trifluoromethane and alkali metal trifluoroacetates might be the best CF_3 sources. However, trifluoromethane is notorious for quick decomposition to difluorocarbene upon deprotonation, whereas alkali metal trifluoroacetates are hygroscopic and poorly soluble in solvents that are suitable for the trifluoromethylation reactions. It is also worth noting that the formation of CuCF_3 species from trifluoroacetates is accompanied by release of equimolar quantities of CO_2 . In order to achieve good yields, trifluoroacetic acid derivatives are conventionally used in large excess, up to 10-fold. Developing an efficient trifluoromethylation process that employs no or little excess of trifluoroacetate is certainly desirable.

There is little doubt that research in the area of aromatic trifluoromethylation and perfluoroalkylation with metal promoters and catalysts will continue and intensify. Being both scientifically exciting and demand-driven, this direction for

research is highly appealing. The scientific community is likely to witness significant advances in this field in the near future.

8. LATEST DEVELOPMENTS

Since this manuscript was submitted for publication, new interesting reports on aromatic trifluoromethylation have appeared in the literature. Buchwald et al.³⁵⁶ reported trifluoromethylation of aryl and heteroaryl boronic acids. This method is similar to the one communicated just a few months earlier by Chu and Qing³³³ but has considerable advantages. First, the reaction³⁵⁶ proceeds at ambient temperature and employs inexpensive $\text{Cu}(\text{OAc})_2$ rather than air-sensitive and much more costly $[\text{Cu}(\text{OTf})] \cdot \text{C}_6\text{H}_6$ used by Chu and Qing.³³³ Second, the amount of Ruppert's reagent needed can be reduced to 2 equiv³⁵⁶ from 5 equiv.³³³ Finally, oxygen is used as reoxidant³⁵⁶ instead of Ag_2CO_3 .³³³ The yields are moderate to good for both electron-rich and electron-deficient aryls.³⁵⁶ Selected examples are presented in Scheme 53.

Xiao and co-workers³⁵⁷ found that CuCF_3 reagents can be generated from (trifluoromethyl)diphenylsulfonium triflate and copper powder. Although trifluoromethylsulfonium salts are electrophilic reagents and a source of " CF_3^+ ", in this case they were used to produce copper complexes for nucleophilic fluorination of a broad variety of heteroaromatic iodides in excellent isolated yields of up to 98%, as shown in Scheme 54 (selected examples).

Goossen et al.³⁵⁸ successfully trifluoromethylated a number of electron-rich and electron-deficient iodoarenes in good to excellent yield with previously designed and developed³⁵⁹ $\text{K}[\text{CF}_3\text{B}(\text{OMe})_3]$ in the presence of CuI/phen (20 mol %). The (trifluoromethyl)trimethoxyborate salt is prepared in virtually quantitative yield from Ruppert's reagent and $\text{KF}^{358,359}$ and has the advantage of being a nonvolatile solid that can be conveniently used at elevated temperatures. Ruppert's reagent itself is a volatile liquid and therefore, in order to avoid losses, has to be used in closed systems at temperatures around its boiling point (54–55 °C) and above. Selected examples of the Cu-catalyzed trifluoromethylation with $\text{K}[\text{CF}_3\text{B}(\text{OMe})_3]$ are presented in Scheme 55.

Also recently, the first efficient system was discovered³⁶⁰ for direct, one-step cupration of fluoroform in high yield at room temperature and atmospheric pressure. Previous attempts to directly cuprate or zincate CF_3H were unsuccessful.⁸⁵ It has now been found³⁶⁰ that treatment of CuX ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) with 2 equiv of an alkali metal alkoxide gives rise to complexes that cuprate fluoroform in a highly selective manner. Thus, reacting CuCl and $t\text{-BuOM}$ ($\text{M} = \text{Na}$ or K) in a 1:2 molar ratio in NMP or DMF, followed by addition of fluoroform (all at room temperature), produces a CuCF_3 complex (^{19}F NMR: s, -23.4 ppm) in >90% yield, as calculated on the amount of CuCl used. The CuCF_3 compound produced this way readily trifluoromethylates iodoarenes at 25–60 °C and may be used for CF_3 transfer to other electrophiles. Interestingly, $[t\text{-BuOCu}]_4$ ^{361–363} that is known^{361,362} to metalate some C–H acids does not react with CF_3H under similar conditions. The newly found cupration reaction of fluoroform exhibits no signs of difluorocarbene intermediacy, nor hemiaminolate formation if performed in DMF (see section 2 and eq 2).³⁶⁰

AUTHOR INFORMATION

Corresponding Author

*E-mail: vgrushin@iciq.es.

BIOGRAPHIES



Olesya Tomashenko obtained her Diploma (2006) and Ph.D. degree (2009) from the St. Petersburg State University. In her Ph.D. work under Dr. Victor Sokolov's supervision, she discovered and subsequently developed a new chemical reaction, the Ti(IV)-catalyzed double addition of Grignard and organolithium reagents to alkyl- and aryl nitriles for the direct, one-step synthesis of primary *tert*-alkylamines. During her graduate studies she also spent 9 months doing research in Prof. Dr. Armin de Meijere's laboratory at The Institute of Organic and Biomolecular Chemistry of The University of Göttingen, Germany. She is currently a Postdoctoral Research Associate in Vladimir Grushin's group at The Institute of Chemical Research of Catalonia (ICIQ) in Tarragona, Spain, working in the area of organometallic fluorine chemistry.



Vladimir Grushin, a native of Moscow, Russia, obtained his Ph.D. degree from Moscow State University (1984). He then spent several years doing research at the Institute of Organo-Element Compounds of the Russian Academy of Sciences and at the University of Ottawa before joining the faculty at Wilfrid Laurier University, Ontario, Canada. In 1997, he took a research position at DuPont CR&D in Wilmington, DE. After 12 years with DuPont, he returned to academia in 2010 with an appointment as Senior Group Leader at The Institute of Chemical Research of Catalonia (ICIQ) in Tarragona, Spain. His research interests span organic and inorganic chemistry, including catalysis and organometallic fluorine chemistry.

ACKNOWLEDGMENT

We thank Prof. Stuart Macgregor (Heriot-Watt University) and Drs. Alexander Kolomeitsev (ChemTaurus GmbH) and

Viacheslav Petrov (DuPont) for discussions and for valuable comments. The ICIQ Foundation and Consolider Ingenio 2010 (Grant CSD2006-0003) are thankfully acknowledged for support.

ABBREVIATIONS

Ac	acetyl
Alk	alkyl
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOXAM	bis[2-((4 <i>S</i>)-4,5-dihydro-4-isopropylloxazol-2-yl)-phenyl]amine
bpy	2,2'-bipyridyl
BrettPhos	dicyclohexyl[3,6-dimethoxy-2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine
Bz	benzoyl
bzq	benzo[<i>h</i>]quinoline (cyclometalated)
Bu	butyl
Cp	cyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
dippe	1,2-bis(diisopropylphosphino)ethane
dipp	1,3-bis(diisopropylphosphino)propane
DMAC	dimethylacetamide
DMF	dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMSO	dimethyl sulfoxide
dppbz	1,2-bis(diphenylphosphino)benzene
dppe	1,2-bis(diphenylphosphino)ethane
dppeO	1,2-bis(diphenylphosphino)ethane monoxide
dppp	1,3-bis(diphenylphosphino)propane
ESCA	electron spectroscopy for chemical analysis
Et	ethyl
Hex	hexyl
HMPA	hexamethylphosphoramide
IPr	1,3-bis(2,6-diisopropylphenyl)imidazolyldiene
Me	methyl
NMP	<i>N</i> -methylpyrrolidone
c-Pent	cyclopentyl
Ph	phenyl
phen	1,10-phenanthroline
PPN	bis(triphenylphosphine)iminium
Pr	propyl
R _f	perfluoroalkyl
RuPhos	[2',6'-bis(1-methylethoxy)[1,1'-biphenyl]-2-yl]dicyclohexylphosphine
SIIPr	1,3-bis(1-methylethyl)-2-imidazolidinylidene
SIMes	1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene
SIPr	1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene
t-Bu-bpy	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridyl
teeda	<i>N,N,N',N'</i> -tetraethyl-1,2-diaminoethane
TfO	triflate (trifluoromethanesulfonate)
tmeda	<i>N,N,N',N'</i> -tetramethyl-1,2-diaminoethane

Tol	tolyl (methylphenyl)
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

REFERENCES

- (1) Pavri, N. *Speciality Chem. Mag.* **2007**, 27, 44.
- (2) Hagmann, W. K. *J. Med. Chem.* **2008**, 51, 4359.
- (3) Jeschke, P. *Pest Manage. Sci.* **2010**, 66, 10.
- (4) Banks, R. E. *Organofluorine Chemicals and Their Industrial Applications*; Ellis Harwood: West Sussex, U.K., 1979.
- (5) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, U.K., 2009.
- (6) Cheng, Y.; Guo, A.-L.; Guo, D.-S. *Curr. Org. Chem.* **2010**, 14, 977.
- (7) Daniels, S.; Tohid, S. F. M.; Velanguparackel, W.; Westwell, A. D. *Expert Opin. Drug Discovery* **2010**, 5, 291.
- (8) Acena, J. L.; Simon-Fuentes, A.; Fustero, S. *Curr. Org. Chem.* **2010**, 14, 928.
- (9) (a) Farinola, G. M.; Cardone, A.; Babudri, F.; Martinelli, C.; Naso, F.; Bruno, G.; Losurdo, M. *Materials* **2010**, 3, 3077. (b) Hird, M. *Chem. Soc. Rev.* **2007**, 36, 2070. (c) Kirsch, P.; Bremer, M. *Angew. Chem., Int. Ed.* **2000**, 39, 4216.
- (10) Fustero, S.; Sanz-Cervera, J. F.; Acena, J. Luis; Sanchez-Rosello, M. *Synlett* **2009**, 525.
- (11) Filler, R.; Saha, R. *Future Med. Chem.* **2009**, 1, 777.
- (12) Kirk, K. L. *Org. Process Res. Dev.* **2008**, 12, 305.
- (13) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, 37, 308. (b) O'Hagan, D. *J. Fluorine Chem.* **2010**, 131, 1071.
- (14) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, 37, 320.
- (15) Shah, P.; Westwell, A. D. *J. Enzyme Inhib. Med. Chem.* **2007**, 22, 527.
- (16) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, 317, 1881.
- (17) Theodoridis, G. *Adv. Fluorine Sci.* **2006**, 2, 121.
- (18) Lehmann, F. *Arch. Exptl. Path. Pharmacol.* **1928**, 130, 250.
- (19) Yale, H. L. *J. Med. Pharm. Chem.* **1959**, 1, 121.
- (20) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, U.K., 2006.
- (21) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004.
- (22) Clark, J. H.; Wails, D.; Bastock, T. W. *Aromatic Fluorination*; CRC Press: Boca Raton, FL, 1996.
- (23) Petrov, V. A. *Fluorinated Heterocyclic Compounds. Synthesis, Chemistry and Applications*; Wiley: Hoboken, NJ, 2009.
- (24) Lopez, S. E.; Restrepo, J.; Salazar, J. *Curr. Org. Synth.* **2010**, 7, 414.
- (25) Boechat, N.; Bastos, M. M. *Curr. Org. Synth.* **2010**, 7, 403.
- (26) Elwahy, A. H. M.; Shaaban, M. R. *Curr. Org. Synth.* **2010**, 7, 433.
- (27) Mloston, G.; Obijalska, E.; Heimgartner, H. *J. Fluorine Chem.* **2010**, 131, 829.
- (28) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, 6, 1219.
- (29) Sato, K.; Tarui, A.; Omote, M.; Ando, A.; Kumadaki, I. *Synthesis* **2010**, 1865.
- (30) Muzalevskiy, V. M.; Shastin, A. V.; Balenkova, E. S.; Haufe, G.; Nenajdenko, V. G. *Synthesis* **2009**, 23, 3905.
- (31) Portella, C.; Grellepois, F.; Massicot, F.; Nonnenmacher, J. *Chim. Oggi* **2009**, 27, 50.
- (32) Davis, C. R.; Burton, D. J. In *Chemistry of Organocopper Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley & Sons: Chichester, 2009.
- (33) Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, 41, 817.
- (34) Makosza, M.; Loska, R. *Z. Naturforsch. B* **2008**, 63, 363.
- (35) Medebielle, M.; Dolbier, W. R., Jr. *J. Fluorine Chem.* **2008**, 129, 930.
- (36) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, 128, 975.

- (37) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921.
- (38) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432.
- (39) Langlois, B. R.; Billard, T.; Roussel, S. *J. Fluorine Chem.* **2005**, *126*, 173.
- (40) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214.
- (41) (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119; **2008**, *108*, PR1. (b) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455.
- (42) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.
- (43) Burton, D. J.; Lu, L. *Top. Curr. Chem.* **1997**, *193*, 45.
- (44) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *32*, 6555.
- (45) Burton, D. J.; Yang, Z. Y. *Tetrahedron* **1992**, *48*, 189.
- (46) Yagupol'skii, L. M.; Il'chenko, A. Ya.; Gandel'sman, L. Z. *Usp. Khim.* **1983**, *52*, 1732.
- (47) Hughes, R. P. *Adv. Organomet. Chem.* **1990**, *31*, 183.
- (48) Morrison, J. A. *Adv. Organomet. Chem.* **1993**, *35*, 211.
- (49) Swarts, F. *Bull. Akad. R. Belg.* **1898**, *35*, 375.
- (50) Daudt, H. W.; Yoker, M. A. U.S. Patent 2005705, 1935 (Filed September 20, 1930).
- (51) Osswald, P.; Müller, F.; Steinhäuser, F. DE 575593, 1933 (Filed November 10, 1931).
- (52) (a) Filler, R. *Adv. Fluorine Chem.* **1970**, *6*, 1. (b) Boswell, G. A., Jr.; Ripka, W. C.; Scribner, R. M.; Tullock, C. W. *Org. React.* **1974**, *21*, 1.
- (53) (a) Tiers, G. V. D. *J. Am. Chem. Soc.* **1960**, *82*, 5513. (b) Drysdale, J. J.; Coffman, D. D. *J. Am. Chem. Soc.* **1960**, *82*, 5111.
- (54) (a) Dolbier, W. R., Jr. *Chem. Rev.* **1996**, *96*, 1557. (b) Furin, G. G. *Russ. Chem. Rev.* **2000**, *69*, 491. (c) Fuchikami, T.; Ojima, I. *J. Fluorine Chem.* **1983**, *22*, 541. (d) Wakselman, C.; Tordeux, M. European Patent Appl. 206951, 1986. (e) Wakselman, C.; Tordeux, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1701. (f) Tordeux, M.; Langlois, B.; Wakselman, C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2293. (g) Moreno-Manas, M.; Pleixats, R.; Villarroya, S. *Synlett* **1999**, 1996. (h) Li, Y.; Li, C.; Yue, W.; Jiang, W.; Kopecek, R.; Qu, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2374. (i) Kino, T.; Nagase, Y.; Ohtsuka, Y.; Yamamoto, K.; Uruguchi, D.; Tokuhisa, K.; Yamakawa, T. *J. Fluorine Chem.* **2010**, *131*, 98.
- (55) McLoughlin, V. C. R.; Thrower, J. U.S. Patent 3408411, 1968.
- (56) McLoughlin, V. C. R.; Thrower, J. *Tetrahedron* **1969**, *25*, 5921.
- (57) Kobayashi, Y.; Kumadaki, I. *Tetrahedron Lett.* **1969**, 4095.
- (58) Fors, B. P. *Metal-Mediated Trifluoromethylation of Aryl Halides*. See: http://www.organicdivision.org/ama/orig/Fellowship/2009_2010_Awardees/Essays/Fors.pdf
- (59) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 12644.
- (60) Dubinina, G. G.; Furutachi, H.; Vicić, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 8600.
- (61) Inoue, M.; Araki, K.; Kawada, K. JP 2009-234921, 2009.
- (62) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909.
- (63) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679.
- (64) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648.
- (65) (a) Lundgren, R. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9322. (b) Ritter, T. *Nature* **2010**, *466*, 447.
- (66) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160.
- (67) (a) Yi, J.-b.; Yan, J. *Youjifu Gongye* **2008**, *31*. (b) Yan, J.; Yi, J.-b. *Sichuan Ligong Xueyuan Xuebao, Ziran Kexueban* **2009**, *22*, 62. (c) Shibata, N.; Furukawa, T. *Kagaku (Kyoto, Japan)* **2009**, *64*, 66. (d) Inoue, M.; Araki, K. *Fain Kemikaru* **2011**, *40*, 40.
- (68) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465.
- (69) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757.
- (70) Haas, A. *J. Fluorine Chem.* **1999**, *100*, 21.
- (71) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195.
- (72) (a) Kruse, A.; Siegemund, G.; Schumann, D. C. A.; Ruppert, I. *Ger. Offen.* DE 3805534, 1989. (b) Kruse, A.; Siegemund, G.; Schumann, D. C. A. U.S. Patent 4968848, 1990.
- (73) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393.
- (74) (a) Stahly, G. P. U.S. Patents 4804772, 4804773, 4804774, and 4845258, 1989. (b) Stahly, G. P.; Bell, D. R. *J. Org. Chem.* **1989**, *54*, 2873.
- (75) Furin, G. G. *Russ. J. Org. Chem.* **1997**, *33*, 1209.
- (76) Prakash, G. K. S.; Hu, J. *ACS Symp. Ser.* **2005**, 911, 16.
- (77) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123.
- (78) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613.
- (79) Prakash, G. K. S.; Yudin, A. K.; Deffieux, D.; Olah, G. A. *Synlett* **1996**, 151.
- (80) Huang, D.; Caulton, K. G. *J. Am. Chem. Soc.* **1997**, *119*, 3185.
- (81) Matsui, K.; Tobita, E.; Ando, M.; Kondo, K. *Chem. Lett.* **1981**, 1719.
- (82) Langlois, B. R.; Roques, N. *J. Fluorine Chem.* **2007**, *128*, 1318.
- (83) Rozen, S.; Hagooly, A. *e-EROS Encyclopedia of Reagents for Organic Synthesis*; 2001; <http://www3.interscience.wiley.com/cgi-bin/mrwhome/104554785/HOME>
- (84) Folleas, B.; Marek, I.; Normant, J.-F.; Saint-Jalmes, L. *Tetrahedron Lett.* **1998**, *39*, 2973.
- (85) Folleas, B.; Marek, I.; Normant, J.-F.; Saint-Jalmes, L. *Tetrahedron* **2000**, *56*, 275.
- (86) Prakash, G. K. S.; Hu, J.; Olah, G. A. *Org. Lett.* **2003**, *5*, 3253.
- (87) Valentine, R. H.; Brodale, G. E.; Giaque, W. F. *J. Phys. Chem.* **1962**, *66*, 392.
- (88) Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. *J. Org. Chem.* **1991**, *56*, 2.
- (89) Barhdadi, R.; Troupel, M.; Perichon, J. *Chem. Commun.* **1998**, 1251.
- (90) Russell, J.; Roques, N. *Tetrahedron* **1998**, *54*, 13771.
- (91) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848.
- (92) Billard, T.; Bruns, S.; Langlois, B. R. *Org. Lett.* **2000**, *2*, 2101.
- (93) Langlois, B. R.; Billard, T. *ACS Symp. Ser.* **2005**, 911, 57.
- (94) Symons, E. A.; Clermont, M. *J. Am. Chem. Soc.* **1981**, *103*, 3127.
- (95) Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014.
- (96) MacNeil, J. G., Jr.; Burton, D. J. *J. Fluorine Chem.* **1991**, *55*, 225.
- (97) Su, D.; Duan, J.; Chen, Q. *Tetrahedron Lett.* **1991**, *32*, 7689.
- (98) (a) Duan, J.; Su, D.; Chen, Q. *J. Fluorine Chem.* **1993**, *61*, 279. (b) Duan, J.; Su, D.; Wu, J.; Chen, Q. *J. Fluorine Chem.* **1994**, *66*, 167.
- (99) Chen, Q.-Y. *e-EROS Encyclopedia of Reagents for Organic Synthesis*; 2001; <http://www3.interscience.wiley.com/cgi-bin/mrwhome/104554785/HOME>
- (100) Chen, Q.; Wu, S. *J. Chem. Soc., Chem. Commun.* **1989**, 705.
- (101) McReynolds, K. A.; Lewis, R. S.; Ackerman, L. K. G.; Dubinina, G. G.; Brennessel, W. W.; Vicić, D. A. *J. Fluorine Chem.* **2010**, *131*, 1108.
- (102) For The Montreal Protocol on Substances that Deplete the Ozone Layer, see: http://ozone.unep.org/Publications/MP_Handbook/Section_1.1_The_Montreal_Protocol/
- (103) Seebach, D. *Angew. Chem., Int. Ed.* **1990**, *29*, 1320.
- (104) Brothers, P. J.; Roper, W. R. *Chem. Rev.* **1988**, *88*, 1293.
- (105) Stone, F. G. A. *J. Fluorine Chem.* **1999**, *100*, 227.
- (106) Hughes, R. P. *Eur. J. Inorg. Chem.* **2009**, 4591.
- (107) See, for example: (a) Yokozeki, A.; Bauer, S. H. *Top. Curr. Chem.* **1975**, *53*, 71. (b) Brauer, D. J.; Bürger, H.; Eujen, R. *J. Organomet. Chem.* **1977**, *135*, 281. (c) Liao, M.-S.; Huang, S.-P. D. *J. Organomet. Chem.* **2000**, *598*, 374.
- (108) (a) Klabunde, K. J.; Key, M. S.; Low, J. Y. F. *J. Am. Chem. Soc.* **1972**, *94*, 999. (b) Klabunde, K. J.; Low, J. Y. F.; Efner, H. F. *J. Am. Chem. Soc.* **1974**, *96*, 1984. (c) Klabunde, K. J.; Low, J. Y. F. *J. Am. Chem. Soc.* **1974**, *96*, 7674. (d) Klabunde, K. J. *Angew. Chem.* **1975**, *87*, 309. (e) Klabunde, K. J.; Anderson, B. B.; Neuenschwander, K. *Inorg. Chem.* **1980**, *19*, 3719.
- (109) (a) Lagow, R. J.; Gerchman, L. L.; Jacob, R. A.; Morrison, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 518. (b) Eujen, R.; Lagow, R. J. *Inorg. Chem.*

- 1975, 14, 3128. (c) Firsich, D. W.; Lagow, R. J. *J. Chem. Soc., Chem. Commun.* **1981**, 1283.
- (110) (a) Emeleus, H. J.; Haszeldine, R. N. *J. Chem. Soc.* **1949**, 2948. (b) Emeleus, H. J.; Haszeldine, R. N. *J. Chem. Soc.* **1949**, 2953.
- (111) (a) Blake, D. M.; Shields, S.; Wyman, L. *Inorg. Chem.* **1974**, 13, 1595. (b) Greene, T. R.; Roper, W. R. *J. Organomet. Chem.* **1986**, 299, 245.
- (112) Hughes, R. P.; Overby, J. S.; Williamson, A.; Lam, K.-C.; Concolino, T. E.; Rheingold, A. L. *Organometallics* **2000**, 19, 5190.
- (113) (a) Krause, L. J.; Morrison, J. A. *J. Am. Chem. Soc.* **1981**, 103, 2995. (b) Krause, L. J.; Morrison, J. A. *J. Chem. Soc., Chem. Commun.* **1981**, 1282. (c) Nair, H. K.; Morrison, J. A. *Inorg. Chem.* **1989**, 28, 2816. (d) Galiotos, J. K.; Morrison, J. A. *Organometallics* **2000**, 19, 2603.
- (114) Kremlev, M. M.; Tyrra, W.; Mushta, A. I.; Naumann, D.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2010**, 131, 212.
- (115) Taw, F. L.; Scott, B. L.; Kiplinger, J. L. *J. Am. Chem. Soc.* **2003**, 125, 14712.
- (116) Vicente, J.; Gil-Rubio, J.; Guerrero-Leal, J.; Bautista, D. *Organometallics* **2004**, 23, 4871.
- (117) (a) Coffield, T. H.; Kozikowski, J.; Closson, R. D. *International Conference on Coordination Chemistry (London, 1959)*; Burlington House: London, 1959; p 126 (abstract) (as cited in ref 48). (b) Closson, R. D.; Coffield, T. H. U.S. Patent 3256306, 1966.
- (118) (a) Knunyants, I. L.; Komissarov, Ya. F.; Dyatkin, B. L.; Lantseva, L. T. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, 943. (b) Eujen, R. *Inorg. Synth.* **1986**, 24, 52.
- (119) Frenking, G.; Fröhlich, N. *Chem. Rev.* **2000**, 100, 717.
- (120) (a) Goodman, J.; Grushin, V. V.; Larichev, R. B.; Macgregor, S. A.; Marshall, W. J.; Roe, D. C. *J. Am. Chem. Soc.* **2009**, 131, 4236. (b) Goodman, J.; Grushin, V. V.; Larichev, R. B.; Macgregor, S. A.; Marshall, W. J.; Roe, D. C. *J. Am. Chem. Soc.* **2010**, 132, 12013.
- (121) Grushin, V. V.; Alper, H. *Organometallics* **1993**, 12, 3846.
- (122) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, 91, 165.
- (123) Loutfy, R. O.; Loutfy, R. O. *Can. J. Chem.* **1976**, 54, 1454.
- (124) Brockway, D. J.; West, B. O.; Bond, A. M. *J. Chem. Soc., Dalton Trans.* **1979**, 1891.
- (125) Kieltsch, L.; Dubinina, G. G.; Hamacher, C.; Kaiser, A.; Torres-Nieto, J.; Hutchison, J. M.; Klein, A.; Budnikova, Yu.; Vivic, D. A. *Organometallics* **2010**, 29, 1451.
- (126) (a) Appleton, T. G.; Clark, H. C.; Manzer, L. E. *J. Organomet. Chem.* **1974**, 65, 275. (b) Appleton, T. G.; Hall, J. R.; Neale, D. W.; Williams, M. A. *J. Organomet. Chem.* **1984**, 276, C73. (c) Appleton, T. G.; Berry, R. D.; Hall, J. R.; Neale, D. W. *J. Organomet. Chem.* **1988**, 342, 399.
- (127) Willert-Porada, M. A.; Burton, D. J.; Baenziger, N. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1633.
- (128) (a) Naumann, D.; Roy, T.; Tebbe, K. F.; Crump, W. *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 1482. (b) Naumann, D.; Tyrra, W.; Trinius, F.; Wessel, W.; Roy, T. *J. Fluorine Chem.* **2000**, 101, 131.
- (129) Menjón, B.; Martínez-Salvador, S.; Gómez-Saso, M. A.; Fornies, J.; Falvello, L. R.; Martín, A.; Tsipis, A. *Chem.—Eur. J.* **2009**, 15, 6371.
- (130) Appleton, T. G.; Chisholm, M. H.; Clark, H. C.; Manzer, L. E. *Inorg. Chem.* **1972**, 11, 1786.
- (131) Appleton, T. G.; Clark, H. C.; Manzer, L. E. *Coord. Chem. Rev.* **1973**, 10, 335.
- (132) Bennett, M. A.; Chee, H.-K.; Robertson, G. B. *Inorg. Chem.* **1979**, 18, 1061.
- (133) Bennett, M. A.; Chee, H.-K.; Jeffery, J. C.; Robertson, G. B. *Inorg. Chem.* **1979**, 18, 1071.
- (134) Hughes, R. P.; Meyer, M. A.; Tawa, M. D.; Ward, A. J.; Williamson, A.; Rheingold, A. L.; Zakharov, L. N. *Inorg. Chem.* **2004**, 43, 747.
- (135) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, 128, 4632.
- (136) Michelin, R. A.; Belluco, U.; Ros, R. *Inorg. Chim. Acta* **1977**, 24, L33.
- (137) Landis, C. R.; Cleveland, T.; Firman, T. K. *J. Am. Chem. Soc.* **1998**, 120, 2641.
- (138) Mitoraj, M. P.; Zhu, H.; Michalak, A.; Ziegler, T. *Int. J. Quantum Chem.* **2009**, 109, 3379.
- (139) Anastasi, A. E.; Deeth, R. J. *J. Chem. Theor. Comp.* **2009**, 5, 2339.
- (140) Huang, H.; Rheingold, A. L.; Hughes, R. P. *Organometallics* **2010**, 29, 3672.
- (141) Holtz, D. *Chem. Rev.* **1971**, 71, 139.
- (142) Yang, D. S.; Bancroft, G. M.; Puddephatt, R. J.; Tse, J. S. *Inorg. Chem.* **1990**, 29, 2496.
- (143) Huang, H.; Hurubeanu, N. R.; Bourgeois, C. J.; Cheah, S.-M.; Yuan, J.; Rheingold, A. L.; Hughes, R. P. *Can. J. Chem.* **2009**, 87, 151.
- (144) Huang, H.; Hughes, R. P.; Rheingold, A. L. *Organometallics* **2010**, 29, 1948.
- (145) Leyssens, T.; Peeters, D.; Orpen, A. G.; Harvey, J. N. *Organometallics* **2007**, 26, 2637.
- (146) Hall, M. B.; Fenske, R. F. *Inorg. Chem.* **1972**, 11, 768.
- (147) Holmes, S. A.; Thomas, T. D. *J. Am. Chem. Soc.* **1975**, 97, 2337.
- (148) Taft, R. W.; Brownlee, R. T. C. *J. Am. Chem. Soc.* **1970**, 92, 7007.
- (149) Nelson, G. L.; Levy, G. C.; Cargioli, J. D. *J. Am. Chem. Soc.* **1972**, 94, 3089.
- (150) Jullien, J.; Martin-Christol, A. L.; Stahl-Larivière, H. *Tetrahedron* **1976**, 32, 1117.
- (151) Levy, J. B. *Struct. Chem.* **1999**, 10, 121.
- (152) Pople, J. A.; Gordon, M. J. *Am. Chem. Soc.* **1967**, 89, 4253.
- (153) Davis, D. W.; Banna, M. S.; Shirley, D. A. *J. Chem. Phys.* **1974**, 60, 237.
- (154) Palmer, M. H. *J. Mol. Struct.* **2000**, 500, 225.
- (155) Chipot, C.; Angyan, J. G.; Ferenczy, G. G.; Scheraga, H. A. *J. Phys. Chem.* **1993**, 97, 6628.
- (156) Nolan, E. M.; Linck, R. G. *J. Phys. Chem. A* **2002**, 106, 533.
- (157) Aktaev, N. P.; Il'in, G. F.; Sokol'skii, G. A.; Knunyants, I. L. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1977**, 1112.
- (158) Macgregor, S. A. Supplementary data for ref 120.
- (159) Klopman, G. In *Chemical Reactivity and Reaction Paths*; Klopman, G., Ed.; John Wiley and Sons: New York, 1974; p 55.
- (160) Strömberg, A.; Gropen, O.; Wahlgren, U.; Lindqvist, O. *Inorg. Chem.* **1983**, 22, 1129.
- (161) Chock, P. B.; Halpern, J. J. *Am. Chem. Soc.* **1966**, 88, 3511.
- (162) Bondi, A. J. *Phys. Chem.* **1964**, 68, 441.
- (163) (a) Huheey, J. E. *J. Phys. Chem.* **1965**, 69, 3284. (b) Canich, J. M.; Ludvig, M. M.; Paudler, W. W.; Gard, G. L.; Shreeve, J. M. *Inorg. Chem.* **1985**, 24, 3668. (c) Bergmann, D.; Hinze, J. *Struct. Bonding (Berlin)* **1987**, 66, 145.
- (164) True, J. E.; Thomas, T. D.; Winter, R. W.; Gard, G. L. *Inorg. Chem.* **2003**, 42, 4437.
- (165) Aullón, G.; Alvarez, S. *Theor. Chem. Acc.* **2009**, 123, 67.
- (166) Kondratenko, N. V.; Vechirko, E. P.; Yagupolskii, L. M. *Synthesis* **1980**, 932.
- (167) Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, 108, 832.
- (168) Kuett, A.; Movchun, V.; Rodima, T.; Dansauer, T.; Rusanov, E. B.; Leito, I.; Kaljurand, I.; Koppel, J.; Pihl, V.; Koppel, I.; Ovsjannikov, G.; Toom, L.; Mishima, M.; Medebielle, M.; Lork, E.; Roeschenthaler, G.-V.; Koppel, I. A.; Kolomeitsev, A. A. *J. Org. Chem.* **2008**, 73, 2607.
- (169) Usui, Y.; Noma, J.; Hirano, M.; Komiya, S. *Inorg. Chim. Acta* **2000**, 309, 151.
- (170) Dubinina, G. G.; Ogikubo, J.; Vivic, D. A. *Organometallics* **2008**, 27, 6233.
- (171) Maitlis, P. M.; Stone, F. G. A. *Chem. Ind.* **1962**, 1865.
- (172) Rosevear, D. T.; Stone, F. G. A. *J. Chem. Soc. A* **1968**, 164.
- (173) Foley, S. R.; Shen, H.; Qadeer, U. A.; Jordan, R. F. *Organometallics* **2004**, 23, 600.
- (174) Naumann, D.; Kirij, N. V.; Maggiora, N.; Tyrra, W.; Yagupolskii, Y. L.; Wickleder, M. S. Z. *Anorg. Allg. Chem.* **2004**, 630, 746.
- (175) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, 23, 3398.
- (176) Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, 132, 2878.

- (177) Fraser, S. L.; Antipin, M. Yu.; Khroustalyov, V. N.; Grushin, V. V. *J. Am. Chem. Soc.* **1997**, *119*, 4769.
- (178) Ye, Y.; Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 14682.
- (179) Grushin, V. V. *Chem. Rev.* **2004**, *104*, 1629.
- (180) McBride, D. W.; Stafford, S. L.; Stone, F. G. A. *J. Chem. Soc.* **1963**, 723.
- (181) McBride, D. W.; Dudek, E.; Stone, F. G. A. *J. Chem. Soc.* **1964**, 1752.
- (182) Ashley-Smith, J.; Green, M.; Stone, F. G. A. *J. Chem. Soc. A* **1969**, 3019.
- (183) Rausch, M. D.; Chang, Y. F.; Gordon, H. B. *Inorg. Chem.* **1969**, *8*, 1355.
- (184) Cundy, C. S. *J. Organomet. Chem.* **1974**, *69*, 305.
- (185) Stanley, K.; Zelonka, R. A.; Thomson, J.; Fiess, P.; Baird, M. C. *Can. J. Chem.* **1974**, *52*, 1781.
- (186) Krespan, C. G.; Dixon, D. A. *J. Org. Chem.* **1998**, *63*, 36.
- (187) Churchill, M. R.; O'Brien, T. A. *J. Chem. Soc. A* **1970**, 161.
- (188) Dubinina, G. G.; Brennessel, W. W.; Miller, J. L.; Vicic, D. A. *Organometallics* **2008**, *27*, 3933.
- (189) Kobayashi, Y.; Kumadaki, I.; Sato, S.; Hara, N.; Chikami, E. *Chem. Pharm. Bull.* **1970**, *18*, 2334.
- (190) Kobayashi, Y.; Yamamoto, K.; Asai, T.; Nakano, M.; Kumadaki, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2755.
- (191) Kobayashi, Y.; Kumadaki, I.; Yamamoto, K. *J. Chem. Soc., Chem. Commun.* **1977**, 536.
- (192) Kobayashi, Y.; Kumadaki, I.; Hanzawa, Y. *Chem. Pharm. Bull.* **1977**, *25*, 3009.
- (193) Kobayashi, Y.; Kumadaki, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 661.
- (194) Hosokawa, K.; Inukai, K. *Nippon Kagaku Kaishi* **1976**, 1791.
- (195) Hosokawa, K.; Inukai, K. *Nippon Kagaku Kaishi* **1977**, 1163.
- (196) Hosokawa, K.; Inukai, K. *Nippon Kagaku Kaishi* **1979**, 294.
- (197) Leroy, J.; Wakselman, C.; Lacroix, P.; Kahn, O. *J. Fluorine Chem.* **1988**, *40*, 23.
- (198) Gould, K. J.; Manners, C. N.; Payling, D. W.; Suschitzky, J. L.; Wells, E. *J. Med. Chem.* **1988**, *31*, 1445.
- (199) Kumadaki, I.; Hirai, M.; Koyama, M.; Nagai, T.; Ando, A.; Miki, T. *Synth. Commun.* **1989**, *19*, 173.
- (200) Koyama, M.; Takagi, T.; Ando, A.; Kumadaki, I. *Chem. Pharm. Bull.* **1995**, *43*, 1466.
- (201) Broka, C. A.; Carter, D. S.; Dillon, M. P.; Hawley, R. C.; Jahangir, A.; Lin, C. J. J.; Parish, D. W. U. S. Patent Appl. 7858632, 2010.
- (202) Jones, P.; Williams, P. D.; Morrisette, M. M.; Kuo, M. S.; Vacca, J. P. PCT Int. Appl. WO 2005/074513, 2005.
- (203) Potashman, M. H.; Bready, J.; Coxon, A.; DeMelfi, T. M.; DiPietro, L.; Doerr, N.; Elbaum, D.; Estrada, J.; Gallant, P.; Germain, J.; Gu, Y.; Harmange, J.-C.; Kaufman, S. A.; Kendall, R.; Kim, J. L.; Kumar, G. N.; Long, A. M.; Neervannan, S.; Patel, V. F.; Polverino, A.; Rose, P.; van der Plas, S.; Whittington, D.; Zanon, R.; Zhao, J. *J. Med. Chem.* **2007**, *50*, 4351.
- (204) Kobayashi, Y.; Kumadaki, I. *Chem. Pharm. Bull.* **1972**, *20*, 1839.
- (205) Yamashita, J.; Matsumoto, H.; Kobayashi, K.; Noguchi, K.; Yasumoto, M.; Ueda, T. *Chem. Pharm. Bull.* **1989**, *37*, 2287.
- (206) Paratian, J. M.; Sibille, S.; Perichon, J. J. *J. Chem. Soc., Chem. Commun.* **1992**, 53.
- (207) (a) Clark, J. H.; McClinton, M. A.; Blade, R. J. *J. Chem. Soc., Chem. Commun.* **1988**, 638. (b) Clark, J. H.; Denness, J. E.; McClinton, M. A.; Wynd, A. J. *J. Fluorine Chem.* **1990**, *50*, 411.
- (208) Clark, J. H.; McClinton, M. A.; Jones, C. W.; Landon, P.; Bishop, D.; Blade, R. J. *Tetrahedron Lett.* **1989**, *30*, 2133.
- (209) Bahner, I.; Lackner, H. *Liebigs Ann.* **1997**, 999.
- (210) Hirai, M.; Kusama, M.; Hosaki, T.; Konhomi, S. PCT Int. Appl. WO 2005/115984, 2005.
- (211) Gopalsamy, A.; Moore, W. J.; Kern, J. C.; Molinari, A. J.; Shi, M.; Welmaker, G. S.; Wilson, M. A.; Krishnamurthy, G.; Commons, T. J.; Webb, M. B.; Woodworth, R. P. Int. Appl. WO 2006/124875, 2006.
- (212) Favor, D. A.; Powers, J. J.; Repine, J. T.; White, A. D. PCT Int. Appl. WO 2008/020306, 2008.
- (213) Commons, T. J.; Mewshaw, R. E.; Moore, W. J.; Kern, J. C.; Webb, M. B. PCT Int. Appl. WO 2008/060999, 2008.
- (214) Moore, W. J.; Kern, J. C.; Bhat, R.; Commons, T. J.; Fukayama, S.; Goljer, I.; Krishnamurthy, G.; Magolda, R. L.; Nogle, L.; Pitts, K.; Stauffer, B.; Trybulski, E. J.; Welmaker, G. S.; Wilson, M.; Bodin, P. V. N. *J. Med. Chem.* **2009**, *52*, 105.
- (215) Suzuki, H.; Yoshida, Y.; Osuka, A. *Chem. Lett.* **1982**, 135.
- (216) Carr, G. E.; Chambers, R. D.; Holmes, T. F.; Parker, D. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 921.
- (217) Mintas, M.; Guesten, H.; Williard, P. G. *J. Photochem. Photobiol. A: Chem.* **1989**, *48*, 341.
- (218) Lin, C. H.; Haadsma, S. R.; Piercey, M. F.; Romero, A. G.; Darlington, W. H. PCT Int. Appl. WO 1990/15047, 1990.
- (219) Le, V. P.; Wells, P. R. *Aust. J. Chem.* **1992**, *45*, 1057.
- (220) (a) Chang, Y.; Cai, C. *Huaxue Shiji* **2005**, *27*, 453. (b) Chang, Y.; Cai, C. *Jingxi Huagong* **2005**, *22*, 311.
- (221) Barbosa, H. J.; Collins, E. A.; Hamdouchi, C.; Hembre, E. J.; Hipskind, P. A.; Johnston, R. D.; Lu, J.; Rupp, M. J.; Takakuwa, T.; Thompson, R. C. U. S. Patent 7612067, 2009.
- (222) (a) Lin, R. W.; Davidson, R. I. Eur. Pat. Appl. EU 307519, 1989. (b) Lin, R. W.; Davidson, R. I. U. S. Patent 4808748, 1989.
- (223) Davidson, R. I. U. S. Patent 4814480, 1989.
- (224) Long, Z.-Y.; Duan, J.-X.; Lin, Y.-B.; Guo, C.-Y.; Chen, Q.-Y. *J. Fluorine Chem.* **1996**, *78*, 177.
- (225) Palmer, K. W.; Resnick, P. R. U. S. Patent 5475165, 1995.
- (226) Qing, F.-L.; Fan, J.; Sun, H.-B.; Yue, X.-J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3053.
- (227) Qing, F.-L.; Fan, J. *J. Fluorine Chem.* **1999**, *96*, 159.
- (228) Veliz, E. A.; Stephens, O. M.; Beal, P. A. *Org. Lett.* **2001**, *3*, 2969.
- (229) Zheng, X.; Meng, W.-D.; Xu, Y.-Y.; Cao, J.-G.; Qing, F.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 881.
- (230) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701.
- (231) Wang, C.-L.; Li, H.-Q.; Meng, W.-D.; Qing, F.-L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4456.
- (232) Grunewald, G. L.; Lu, J.; Criscione, K. R.; Okoro, C. O. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5319.
- (233) Jin, L.-M.; Chen, L.; Yin, J.-J.; Guo, C.-C.; Chen, Q.-Y. *Eur. J. Org. Chem.* **2005**, 3994.
- (234) De Angelis, M.; Stossi, F.; Carlson, K. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2005**, *48*, 1132.
- (235) Jin, L.-M.; Chen, L.; Yin, J.-J.; Zhou, J.-M.; Guo, C.-C.; Chen, Q.-Y. *J. Org. Chem.* **2006**, *71*, 527.
- (236) Grunewald, G. L.; Seim, M. R.; Lu, J.; Makboul, M.; Criscione, K. R. *J. Med. Chem.* **2006**, *49*, 2939.
- (237) Romero, F. A.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 14004.
- (238) Lee, J.; Park, T.; Jeong, S.; Kim, K.-H.; Hong, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1284.
- (239) Du, X.; Chen, X.; Mihalic, J. T.; Deignan, J.; Duquette, J.; Li, A.-R.; Lemon, B.; Ma, J.; Miao, S.; Ebsworth, K.; Sullivan, T. J.; Tonn, G.; Collins, T. L.; Medina, J. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 608.
- (240) Kimball, F. S.; Romero, F. A.; Ezzili, C.; Garfunkle, J.; Rayl, T. J.; Hochstatter, D. G.; Hwang, I.; Boger, D. L. *J. Med. Chem.* **2008**, *51*, 937.
- (241) Yeates, C. L.; Batchelor, J. F.; Capon, E. C.; Cheesman, N. J.; Fry, M.; Hudson, A. T.; Pudney, M.; Trimming, H.; Woolven, J.; Bueno, J. M.; Chicharro, J.; Fernandez, E.; Fiandor, J. M.; Gargallo-Viola, D.; Gomez de las Heras, F.; Herreros, E.; Leon, M. L. *J. Med. Chem.* **2008**, *51*, 2845.
- (242) Roy, S.; Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 1128.
- (243) Shibata, K.; Yoshida, M.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2010**, *51*, 1674.
- (244) Heurich, R. PCT Int. Appl. WO 2005/091857, 2005.
- (245) Barrow, J. C.; Mcgaughey, G. B.; Nantermet, P. G.; Rajapakse, H. A.; Selnick, H. G.; Stauffer, S. R.; Coburn, C. A. U. S. Patent 7847100, 2010.

- (246) Aicher, T. D.; Benesh, D. R.; Blanco-Pillado, M.-J.; Cortez, G. S.; Groendyke, T. M.; Khilevich, A.; Knobelsdorf, J. A.; Marmsater, F. P.; Schkeryantz, J. M.; Tang, T. P. *PCT Int. Appl. WO 2006/057860*, 2006.
- (247) Aicher, T. D.; Cortez, G. S.; Groendyke, T. M.; Khilevich, A.; Knobelsdorf, J. A.; Marmsater, F. P.; Schkeryantz, J. M.; Tang, T. P. *PCT Int. Appl. WO 2006/057869*, 2006.
- (248) Matsunaga, N.; Ito, M.; Hitaka, T. *PCT Int. Appl. WO 2006/064944*, 2006.
- (249) Adams, N. D.; Darcy, M. G.; Dhanak, D.; Duffy, K. J.; Fitch, D. M.; Knight, S. D.; Newlander, K. A.; Shaw, A. N. *PCT Int. Appl. WO 2006/113432*, 2006.
- (250) Caldwell, T. M.; Chenard, B.; Hodgetts, K. *PCT Int. Appl. WO 2006/076646*, 2006.
- (251) Briner, K.; Camp, A. M.; Cornell, A.; Mazanetz, M. P.; Rothhaar, R. R.; Victor, F.; Williams, A. C.; Zhang, D. *PCT Int. Appl. WO 2007/028132*, 2007.
- (252) Rockway, T. W.; Betebenner, D. A.; Krueger, A. C.; Iwasaki, N.; Cooper, C. S.; Anderson, D. D.; Kempf, D. J.; Madigan, D. L.; Motter, C. E.; Shanley, J. P.; Tufano, M. D.; Wagner, R.; Zhang, R.; Molla, A.; Mo, H.; Pilot-Matias, T.; Masse, S. V. L.; Carrick, R. J.; He, W.; Lu, L. U. S. Patent 7763731, 2010.
- (253) Ali, A.; Lu, Z.; Sinclair, P. J.; Chen, Y.-H.; Smith, C. J.; Li, H.; Thompson, C. F. *PCT Int. Appl. WO 2007/081569*, 2007.
- (254) Ito, M.; Matsunaga, N.; Yamada, M.; Hitaka, T.; Yamamoto, S. *PCT Int. Appl. WO 2007/145349*, 2007.
- (255) Boger, D. L. *PCT Int. Appl. WO 2008/030532*, 2008.
- (256) Bi, F.; Didiuk, M. T.; Griffith, D. A.; Guzman-Perez, A.; Liu, K. K.-C.; Walker, D. P. *PCT Int. Appl. WO 2008/041118*, 2008.
- (257) Ge, M.; Lin, S.; Walsh, S. P.; Yang, L.; Zhou, C. *PCT Int. Appl. WO 2008/054675*, 2008.
- (258) Le Huerou, Y.; Blake, J. F.; Gunwardana, I. W.; Mohr, P.; Wallace, E. M.; Wang, B.; Chicarelli, M.; Lyon, M. *PCT Int. Appl. WO 2009/140320*, 2009.
- (259) Trabanco-Suarez, A. A.; Tresadern, G. J.; Vega Ramiro, J. A.; Cid-Nunez, J. M. *PCT Int. Appl. WO 2009/062676*, 2009.
- (260) Cid-Nunez, J. M.; Trabanco-Suarez, A. A.; Macdonald, G. J.; Duvey, G. A. J.; Lutjens, R. J.; Finn, T. P. *PCT Int. Appl. WO 2009/033704*, 2009.
- (261) Cid-Nunez, J. M.; Trabanco-Suarez, A. A.; MacDonald, G. J.; Duvey, G. A. J.; Lutjens, R. J.; Finn, T. P. *PCT Int. Appl. WO 2009/033702*, 2009.
- (262) Bakthavatchalam, R.; Ihle, D. C.; Capitosti, S. M.; Wustrow, D. J.; Yuan, J. *PCT Int. Appl. WO 2009/023623*, 2009.
- (263) Bartolome-Nebreda, J. M.; MacDonald, G. J.; Van Gool, M. L. M. *PCT Int. Appl. WO 2010/012758*, 2010.
- (264) Liu, C.; Chen, Q.-Y. *Eur. J. Org. Chem.* **2005**, 3680.
- (265) Liu, C.; Shen, D.-M.; Chen, Q.-Y. *J. Org. Chem.* **2007**, 72, 2732.
- (266) Li, H.; Duan, J.; Su, D.; Chen, Q. *Chin. J. Chem.* **1993**, 11, 366.
- (267) Chen, Q.-Y.; Duan, J.-X. *J. Chem. Soc., Chem. Commun.* **1993**, 1389.
- (268) Wang, Z.-X.; Duan, W.; Wiebe, L. I.; Balzarini, J.; De Clercq, E.; Knaus, E. E. *Nucleosides, Nucleotides Nucleic Acids* **2001**, 20, 11.
- (269) Dade, J.; Provot, O.; Moskowitz, H.; Mayrargue, J.; Prina, E. *Chem. Pharm. Bull.* **2001**, 49, 480.
- (270) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, 125, 12502.
- (271) Bentley, J. M.; Adams, D. R.; Bebbington, D.; Benwell, K. R.; Bickerdike, M. J.; Davidson, J. E. P.; Dawson, C. E.; Dourish, C. T.; Duncton, M. A. J.; Gaur, S.; George, A. R.; Giles, P. R.; Hamlyn, R. J.; Kennett, G. A.; Knight, A. R.; Malcolm, C. S.; Mansell, H. L.; Misra, A.; Monck, N. J. T.; Pratt, R. M.; Quirk, K.; Roffey, J. R. A.; Vickers, S. P.; Cliffe, I. A. *Bioorg. Med. Chem. Lett.* **2004**, 14, 2367.
- (272) Lynch, J. E.; Shi, Y.-J.; Wells, K. M. U. S. Patent Appl. GB 2328942, 1999.
- (273) Hadida Ruah, S. S.; Hazlewood, A. R.; Grootenhuis, P. D. J.; Van Goor, F. F.; Singh, A. K.; Zhou, J.; McCartney, J. *PCT Int. Appl. WO 2006/002421*, 2006.
- (274) Clayton, J.; Ma, F.; Van Wagenen, B.; Ukkiramapandian, R.; Egle, I.; Empfield, J.; Isaac, M.; Slassi, A.; Steelman, G.; Urbaneck, R.; Walsh, S. *PCT Int. Appl. WO 2006/020879*, 2006.
- (275) Zeng, Q.; Yang, D.-Y.; Rosenblum, S. B.; Wong, M. K. C.; Anilkumar, G. N.; Kim, S. H.; Yu, W.; Kozlowski, J. A.; Shih, N.-Y.; McGuinness, B. F.; Zawacki, L. G.; Hobbs, D. W. *PCT Int. Appl. WO 2006/091428*, 2006.
- (276) Bolli, M.; Lehmann, D.; Mathys, B.; Mueller, C.; Nayler, O.; Velker, J.; Weller, T. U. S. Patent 7723378, 2010.
- (277) Bolli, M.; Lehmann, D.; Mathys, B.; Mueller, C.; Nayler, O.; Steiner, B.; Velker, J. *PCT Int. Appl. WO 2007/060626*, 2007.
- (278) Rosenblum, S. B.; Kozlowski, J. A.; Shih, N.-Y.; McGuinness, B. F.; Hobbs, D. W. U. S. Patent 7786124, 2010.
- (279) Kremoser, C.; Deuschle, U.; Abel, U.; Schulz, A. *PCT Int. Appl. WO 2008/025540*, 2008.
- (280) Rosenblum, S. B.; Kozlowski, J. A.; Shih, N.-Y.; McGuinness, B. F.; Hobbs, D. W. *PCT Int. Appl. WO 2008/008453*, 2008.
- (281) Beaulieu, P. L.; Forgione, P.; Gagnon, A.; Godbout, C.; Joly, M.-A.; Llinas-Brunet, M.; Naud, J.; Poirier, M.; Rancourt, J. *PCT Int. Appl. WO 2009/076747*, 2009.
- (282) Sahlberg, C.; Sund, C.; Wikteliu, D.; Belda, O. *PCT Int. Appl. WO 2010/024772*, 2010.
- (283) Chen, Q.-Y.; Wu, S.-W. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2385.
- (284) (a) Umemoto, T.; Ando, A. *Bull. Chem. Soc. Jpn.* **1986**, 59, 447. (b) Umemoto, T. *Yuki Gosei Kagaku Kyokaishi* **1986**, 44, 883.
- (285) Heaton, C. A.; Powell, R. L. *J. Fluorine Chem.* **1989**, 45, 86.
- (286) Yang, Z.-Y.; Burton, D. J. *J. Fluorine Chem.* **2000**, 102, 89.
- (287) Nair, V.; Buenger, G. S. *J. Am. Chem. Soc.* **1989**, 111, 8502.
- (288) Nair, V.; Purdy, D. F.; Sells, T. B. *J. Chem. Soc., Chem. Commun.* **1989**, 878.
- (289) Chauviere, G.; Viode, C.; Perie, J. *J. Heterocycl. Chem.* **2000**, 37, 119.
- (290) Terazono, Y.; Dolphin, D. *J. Org. Chem.* **2003**, 68, 1892.
- (291) (a) Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, 32, 91. (b) Fuchikami, T.; Urata, H. JP 03218325, 1991.
- (292) Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 327.
- (293) Cottet, F.; Schlosser, M. *Tetrahedron* **2004**, 60, 11869.
- (294) Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 3793.
- (295) Cottet, F.; Marull, M.; Mongin, F.; Espinosa, D.; Schlosser, M. *Synthesis* **2004**, 1619.
- (296) Cottet, F.; Castagnetti, E.; Schlosser, M. *Synthesis* **2005**, 798.
- (297) (a) Kitazume, T.; Nakajima, S. *J. Fluorine Chem.* **2004**, 125, 1447. (b) Bardin, V. V.; Kolomeitsev, A. A.; Furin, G. G.; Yagupol'skii, Yu. L. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 1693.
- (298) Mano, T.; Stevens, R. W.; Ando, K.; Nakao, K.; Okumura, Y.; Sakakibara, M.; Okumura, T.; Tamura, T.; Miyamoto, K. *Bioorg. Med. Chem.* **2003**, 11, 3879.
- (299) Nunez, M. C.; Pavani, M. G.; Diaz-Gavilan, M.; Rodriguez-Serrano, F.; Gomez-Vidal, J. A.; Marchal, J. A.; Aranega, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. *Tetrahedron* **2006**, 62, 11724.
- (300) Takizawa, S.-Y.; Nishida, J.-I.; Tsuzuki, T.; Tokito, S.; Yamashita, Y. *Inorg. Chem.* **2007**, 46, 4308.
- (301) Hoefgen, N.; Stange, H.; Schindler, R.; Lankau, H.-J.; Grunwald, C.; Langen, B.; Egerland, U.; Tremmel, P.; Pangalos, M. N.; Marquis, K. L.; Hage, T.; Harrison, B. L.; Malamas, M. S.; Brandon, N. J.; Kronbach, T. *J. Med. Chem.* **2010**, 53, 4399.
- (302) Childers, W. E.; Havran, L. M.; Asselin, M.; Bicksler, J. J.; Chong, D. C.; Grosu, G. T.; Shen, Z.; Abou-Gharbia, M. A.; Bach, A. C.; Harrison, B. L.; Kagan, N.; Kleintop, T.; Magolda, R.; Marathias, V.; Robichaud, A. J.; Sabb, A. L.; Zhang, M.-Y.; Andree, T. H.; Aschmies, S. H.; Beyer, C.; Comery, T. A.; Day, M.; Grauer, S. M.; Hughes, Z. A.; Rosenzweig-Lipson, S.; Platt, B.; Pulicicchio, C.; Smith, D. E.; Sukoff-Rizzo, S. J.; Sullivan, K. M.; Adedoyin, A.; Huselton, C.; Hirst, W. D. *J. Med. Chem.* **2010**, 53, 4066.
- (303) Bruton, G.; Orlek, B. S.; Rana, K. K. U. S. Patent 7592347, 2009.

- (304) Bailey, J. M.; Bruton, G.; Huxley, A.; Milner, P. H.; Orlek, B. S. PCT Int. Appl. WO 2005/014571, 2005.
- (305) Allen, A. J.; Kelsey, D. K. PCT Int. Appl. WO 2005/020976, 2005.
- (306) Clark, B. P.; Gallagher, P. T. U. S. Patent 7488728, 2009.
- (307) Bruton, G.; Huxley, A.; Orlek, B. S.; Rana, K. K. U. S. Patent 7846922, 2010.
- (308) Allen, A. J.; Hemrick-Luecke, S.; Sumner, C. R.; Wallace, O. B. PCT Int. Appl. WO 2005/060949, 2005.
- (309) Wada, K.; Gomibuchi, T.; Yoneta, Y.; Otsu, Y.; Shibuya, K.; Nakakura, N.; Fischer, R. U. S. Patent 7674807, 2010.
- (310) Carroll, W. A.; Perez-Medrano, A.; Florjancic, A. S.; Nelson, D. W.; Peddi, S.; Bunnelle, E. M.; Hirst, G. C.; Li, B. U. S. Patent 7704997, 2010.
- (311) Xue, C.-B.; Zheng, C.; Feng, H.; Xia, M.; Glenn, J.; Cao, G.; Metcalf, B. W. PCT Int. Appl. WO 2006/004741, 2006.
- (312) Smith, A. L.; Brennan, P. E.; Demorin, F. F.; Liu, G.; Paras, N. A.; Retz, D. M. PCT Int. Appl. WO 2006/066172, 2006.
- (313) Asselin, M.; Grosu, G. T.; Sabb, A. L.; Childers, W. E.; Havran, L. M.; Shen, Z.; Bicksler, J. J.; Chong, D. C. PCT Int. Appl. WO 2006/135839, 2006.
- (314) Floersheim, P.; Froestl, W.; Guery, S.; Kaupmann, K.; Koller, M. PCT Int. Appl. WO 2006/136442, 2006.
- (315) Parker, M. F.; Bronson, J. J.; Silva, M. V.; Gillman, K. W. PCT Int. Appl. WO 2008/014247, 2008.
- (316) Lemoine, R.; Melville, C. R.; Rotstein, D.; Wanner, J. U. S. Patent 7625905, 2009.
- (317) Aso, K.; Mochizuki, M.; Kojima, T.; Kobayashi, K.; Pratt, S. A.; Gyorkos, A. C.; Corrette, C. P.; Cho, S. Y. PCT Int. Appl. WO 2008/051533, 2008.
- (318) Allen, J. R.; Biswas, K.; Cao, G.-Q.; Golden, J. E.; Mercede, S.; Peterkin, T.; Reed, A.; Tegley, C. M. PCT Int. Appl. WO 2008/076425, 2008.
- (319) Bentley, J.; Biagetti, M.; Di Fabio, R.; Genski, T.; Guery, S.; Kopf, S. R.; Leslie, C. P.; Mazzali, A.; Melotto, S.; Pizzi, D. A.; Sabbatini, F. M.; Seri, C. PCT Int. Appl. WO 2008/092888, 2008.
- (320) Nagashima, Y.; Kusumoto, T. PCT Int. Appl. WO 2008/111417, 2008.
- (321) Yu, T.; Belanger, D. B.; Kerekes, A. D.; Meng, Z.; Tagat, J. R.; Esposito, S. J.; Mandal, A. K.; Xiao, Y.; Kulkarni, B. A.; Zhang, Y.; Curran, P. J.; Doll, R.; Siddiqui, M. A. PCT Int. Appl. WO 2008/156614, 2008.
- (322) Campos Rosa, J.; Espinosa Ubeda, A.; Gallo Mezo, M. A.; Gomez Vidal, J. A.; Nunez Carretero, M. del C.; Aranega Jimenez, A. ES 2303444, 2008.
- (323) Mizuno, H. PCT Int. Appl. WO 2009/066786, 2009.
- (324) Nichols, P. L.; Sehmi, S. S.; Ward, R. W.; Wilson, D. M. PCT Int. Appl. WO 2009/080682, 2009.
- (325) Adamczewski, M.; Arnold, C.; Becker, A.; Carles, L.; Dahmen, P.; Dunkel, R.; Franken, E.-M.; Goergens, U.; Grosjean-Cournoyer, M.-C.; Helmke, H.; Hillebrand, S.; Hiroyuki, H.; Kluth, J.; Knobloch, T.; Loesel, P.; Nennstiel, D.; Rieck, H.; Rama, R.; Suelmann, R.; Voerste, A.; Wachendorff-Neumann, U. PCT Int. Appl. WO 2010/012793, 2010.
- (326) (a) Ozawa, F.; Kurihara, K.; Fujimori, M.; Hidaka, T.; Toyoshima, T.; Yamamoto, A. *Organometallics* **1989**, *8*, 180. (b) Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta* **1994**, *220*, 249.
- (327) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1982**, 137.
- (328) Koh, P. L.; Foster, A. J. U. K. Patent Appl. GB 2339781, 2000.
- (329) Roche, A. J.; Dolbier, W. R., Jr. *J. Org. Chem.* **1999**, *64*, 9137.
- (330) Roche, A. J.; Dolbier, W. R., Jr. *J. Org. Chem.* **2000**, *65*, 5282.
- (331) Qing, F.-L.; Zhang, X.; Peng, Y. *J. Fluorine Chem.* **2001**, *111*, 185.
- (332) (a) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898. (b) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661. (c) Shen, X.; Hyde, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14076.
- (333) Chu, L.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 5060.
- (334) Gladysz, J. A.; Horvath, I.; Curran, D. P., Eds. *Handbook of Fluorous Chemistry*; Wiley-VCH: Weinheim, 2004.
- (335) Yang, Z.-Y.; Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 4402.
- (336) Leroy, J.; Rubinstein, M.; Wakselman, C. *J. Fluorine Chem.* **1985**, *27*, 291.
- (337) Chen, G. J.; Tamborski, C. *J. Fluorine Chem.* **1989**, *43*, 207.
- (338) Chen, G. J.; Chen, L. S.; Eapen, K. C. *J. Fluorine Chem.* **1993**, *63*, 113.
- (339) Chen, G. J.; Tamborski, C. *J. Fluorine Chem.* **1990**, *46*, 137.
- (340) Paciorek, K. J. L.; Masuda, S. R.; Shih, J. G.; Nakahara, J. H. *J. Fluorine Chem.* **1991**, *53*, 233.
- (341) Chen, G. J.; Chen, L. S.; Eapen, K. C. *J. Fluorine Chem.* **1993**, *65*, 59.
- (342) Bhattacharyya, P.; Gudmunsen, D.; Hope, E., G.; Kemmitt, R. D. W.; Paige, D. R.; Stuart, A. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3609.
- (343) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2000**, *41*, 3697.
- (344) Van den Broeke, J.; Deelman, B.-J.; van Koten, G. *Tetrahedron Lett.* **2001**, *42*, 8085.
- (345) Birdsall, D. J.; Hope, E. G.; Stuart, A. M.; Chen, W.; Hu, Y.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 8551.
- (346) Croxtall, B.; Fawcett, J.; Hope, E. G.; Stuart, A. M. *J. Chem. Soc., Dalton Trans.* **2002**, 491.
- (347) Adams, D. J.; Gudmunsen, D.; Fawcett, J.; Hope, E., G.; Stuart, A. M. *Tetrahedron* **2002**, *58*, 3827.
- (348) Chen, W.; Xu, L.; Hu, Y.; Osuna, A. M. B.; Xiao, J. *Tetrahedron* **2002**, *58*, 3889.
- (349) Adams, D. J.; Gudmunsen, D.; Hope, E., G.; Stuart, A. M.; West, A. *J. Fluorine Chem.* **2003**, *121*, 213.
- (350) Berthod, M.; Mignani, G.; Lemaire, M. *Tetrahedron: Asymmetry* **2004**, *15*, 1121.
- (351) Kim, Y.; Whitten, J. E.; Swager, T. M. *J. Am. Chem. Soc.* **2005**, *127*, 12122.
- (352) Xiao, J.-C.; Ye, C.; Shreeve, J. M. *Org. Lett.* **2005**, *7*, 1963.
- (353) Freskos, J. N. *Synth. Commun.* **1988**, *18*, 965.
- (354) Su, D.-B.; Duan, J.-X.; Yu, A.-J.; Chen, Q.-Y. *J. Fluorine Chem.* **1993**, *65*, 11.
- (355) Burton, D. J.; Wiemers, D. M.; Easdon, J. C. U. S. Patent 4582921, 1986.
- (356) Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. *J. Org. Chem.* **2011**, *76*, 1174.
- (357) Zhang, C.-P.; Wang, Z.-L.; Chen, Q.-Y.; Zhang, C.-T.; Gu, Y.-C.; Xiao, J.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1.
- (358) Knauber, T.; Arian, F.; Rösenthaller, G.-V.; Goossen, L. J. *Chem. Eur. J.* **2011**, *17*, 2689.
- (359) Kolomeitsev, A. A.; Kadyrov, A. A.; Szczepkowska-Sztolcman, J.; Milewska, M.; Koroniak, H.; Bissky, G.; Barten, J. A.; Rösenthaller, G.-V. *Tetrahedron Lett.* **2003**, *44*, 8273.
- (360) (a) Grushin, V. V. Patent application (to ICIQ) filed. (b) Zanardi, A.; Grushin, V. V. Manuscript in preparation.
- (361) Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, *94*, 958.
- (362) Lemmen, T. H.; Goeden, G. V.; Huffman, J. C.; Geerts, R. L.; Caulton, K. G. *Inorg. Chem.* **1990**, *29*, 3680.
- (363) (a) Greiser, T.; Weiss, E. *Chem. Ber.* **1976**, *109*, 3142. (b) Hakansson, M.; Lopes, C.; Jagner, S. *Inorg. Chim. Acta* **2000**, *304*, 178.